Review Article

# Emerging Trends in Novel Drug Delivery System: Intra Nasal Drug Delivery

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**ABSTRACT**

Delivery of drugs through nasal route has been potentially explored as an alternative route for administration of vaccines, hormones and biomolecules such as proteins, peptides and non - peptide drugs. Intranasal therapy has been accepted form of treatment in the ayurvedic system of medicines. Considering the large number of problems associated with oral, parenteral, rectal and other routes of drug administration and gradual increase in interest of pharmaceutical scientists towards exploring the possibilities of intranasal delivery of various drugs. Due to the high permeability, high vasculature, low enzymatic environment of nasal cavity and avoidance of hepatic first pass metabolism are well suitable for systemic delivery of drug molecule via nose. Since nasal mucosa offer several benefits for target drug delivery, a wide variety of therapeutic compounds may be administered intranasally for topical, systemic and central nervous system action. The drugs are administered by nasal delivery devices such as powder devices, liquid devices, semisolid devices etc. The different aspects of nasal anatomy, advantages, disadvantages and ideal properties of nasal drug delivery system, factors affecting nasal absorption, bioavailability barriers, strategies to improve nasal absorption and applications of nasal drug delivery system are discussed in this article.

**Keywords:** Intranasal drug delivery, Bioavailability, devices, applications.

## INTRODUCTION

Drugs are administered traditionally by oral and parenteral routes for systemic delivery. The gastro intestinal tract (GIT) is the major route of drug entry to the systemic circulation. The GIT presents a hostile environment; it contains enzymes, a wide range of pH conditions and varies in its composition depending upon the presence or absence of food. Those drugs which are susceptible to either acid hydrolysis or extensive metabolism in the liver may exhibit poor bioavailability.Drug administered via the parenteral route gain access to systemic circulation directly by producing maximum plasma level but this route is associated with pain and discomfort and can only be given by medical person. In an attempt to circumvent these problems, alternative routes of drug administration are being investigated. Transdermal, rectal, buccal and nasal routes by pass hepatic first pass metabolism and offer alternative routes for the systemic delivery of drugs. However, transdermal does not provide rapid blood level and is limited to controlled delivery of potent lipophillic drugs. The rectal route suffers from variable patient acceptance and depending upon the site of absorption the drug may be subjected to hepatic first pass metabolism. Buccal and sublingual route of drug administration are of much interest, but sometimes pose inconvenience during speaking, eating and drinking. Hence the nasal route holds potential for administration of various drugs with avoidance of first pass metabolism and better bioavailability.[1] Nasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine.[2, 3] In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration.[4]

The history of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects. Nasal therapy also called ‘Nasya karma’ has been recognized form of treatment in the Ayurvedic system of Indian medicines.[5] Intranasal drug delivery offers a

promising alternative route for administration of such drugs.[6,7] In the past decade, the use of the nasal cavity as a route for drug delivery has been an area of great interest to the pharmaceutical industry, especially for systemically acting drugs that are difficult to deliver via routes other than injection.[8] Currently, nasal drug delivery has been recognized as a very promising route for delivery of therapeutic compounds. Conventionally, the nasal route has been used for local delivery of drugs for treating nasal allergy, nasal congestion and nasal infections.[8] The use of nasal pathway for the delivery of drugs is an emerging field in both pharmaceutical sciences and pharmaceutical industry.[9] Nasal route is easily accessible, convenient, and a reliable with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds into the systemic circulation, avoiding the hepatic first pass elimination. In addition, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects.[8,10]

Nasal administration minimizes the lag time associated with oral drug delivery and offers noninvasiveness, self-administration, patient comfort, and patient compliance, which are the hurdles in intravenous drug therapy.[11] Drugs ranging from small chemicals to large macromolecules including peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity.[12]

A range of companies specializing in the development of innovative nasal delivery systems and formulation are actively developing novel nasal formulations for conventional generic drugs (e.g. apomorphine, triptans, morphine, midazolam, fentanyl, non-steroid anti-inflammatory drugs), as well as for peptides and proteins (e.g. leuprolide, parathyroid hormone, insulin, interferon) in situations where the nasal route would be beneficial for the therapeutic efficacy of the drug.[13,14] It has also been considered to the administration of vaccine.[15,16]

Buserelin, desmopressin, calcitonin, insulin, and luteinizing hormone releasing hormone, growth hormone and adreno-corticotrophic hormone are some of the peptides that have been successfully administered through the nasal route. Apart from these, steroids (corticosteroids, estradiol, progesterone, testosterone.etc), [17,18] antihypertensives (nifedipine, nitroglycerine, propranolol, hydralazine.etc), analgesics (buprenorphine), antibiotics and antivirals[19] have been shown to produce considerable systemic effects when administered via the nasal cavity.

Intranasal delivery is currently being employed in treatments for migraine, smoking cessation, acute pain relief, osteoporosis, 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.[20] For nasal drug delivery various systems are also in use: nasal drops as multiple or single-dose formulation, pressurized MDIs, dry powder inhalers, nasal spray, nasal pumps, gels, micro-emulsion, suspensions, powders and thermo reversible muco-adhesive gels.[21]

**ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM**

1. Easy accessibility and needle free drug application without the necessity of trained personnel facilitates self medication, thus improving patient compliances compared to parenteral routes.[22]
2. Good penetration of, especially liphophilic, low molecular weight drugs through the nasal mucosa.[23]
3. Rapid absorption and fast onset of action due to relatively large absorption surface and high vascularization.[23]
4. Avoidance of the harsh environmental conditions in the gastrointestinal tract (chemical and enzymatic degradation of drugs).
5. Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.[24]
6. Potential for direct delivery of drug to the central nervous system via the olfactory region, bypassing the blood brain barrier.[25]
7. Direct delivery of vaccine to lymphatic tissue and induction of a secretory immune response at distant mucosal site.[14]
8. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
9. The nasal bioavailability for smaller drug molecules is good.
10. Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.

11. Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
12. Drugs possessing poor stability in G.I.T fluids are given by nasal route.[26,19]
13. Rich vasculature and highly permeable structure in nasal cavity facilitates more and rapid drug absorption.[2]
14. Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for proteins and peptides.
15. Direct transport into systemic circulation and CNS is possible.
16. Offers lower risk of overdose.
17. Does not have any complex formulation requirement. [26,19]

**Limitations of Nasal Drug Delivery System [27, 28]**

The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.

1. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
2. Nasal cavity provides smaller absorption surface area when compared to GIT.
3. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
4. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
5. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.[29]
6. Irritation of nasal mucosa by drugs like Budesonide &Azilactine.
7. Limited understanding of mechanisms and less developed models at this stage.
8. Delivery volume in nasal cavity is restricted to 25–200 µL.
9. High molecular weight compounds cannot be delivered through this route (mass cut off ~1 kDa).
10. Adversely affected by pathological conditions.
11. Large interspecies variability is observed in this route.[30-32]

**Anatomy and Physiology of Nose**

The nasal route is used for the systemic delivery of medication due to a high degree of vascularization and permeability of the nasal mucosa.[33] In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters the air, heats and humidifies the inhaled air before reaching the lowest airways.[34] Nasal cavity is lined with mucus layer and hairs which are involved in the functions like trapping the inhaled particles and pathogens.

Anatomically human nasal cavity fills the space between the base of the skull and the roof of the mouth. Above mouth, it is supported by the ethamoid bones and laterally by the ethamoid, maxillary and inferior conchae bones.[2] The nasal passage which runs from nasal vestibule to nasopharynx has a depth of approximately 12-14cm. The total surface area of the nasal cavity in human adult is about 150 $cm^2$ and total volume is about 15 ml.[34] The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril.[20]

Each of two nasal cavities can be subdivided into different regions: nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory region, frontal sinus, sphenoidal sinus, and cribriform plate of ethmoid bone. The nasal cavity also contains the NALT, which is mainly situated in the nasopharynx.[35]

The main nasal airway having the narrow passages, usually it has 1-3mm wide and these narrow structures are useful to nose to carry out its main functions.[20]

The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport.[36] The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium; it secretes the mucus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer.[20]

Nasal cavity is divided by middle septum into two symmetrical halves, each one opening at

the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics[35] given in Fig.1 and structural features are explained in Table 1.

**Nasal Vestibule**

Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 $cm^2$.[37] Nasal hairs are present in this area, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands.[38] The vestibular area serve as a baffle system and its surface is covered by a common pseudostratified epithelium where the long hairs may provide the function of filtering air borne particles.[39]

**Atrium**

Intermediate area between nasal vestibule and respiratory region is atrium. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by psudostratified columnar cells presenting microvilli.[40, 41]

**Respiratory Region**

Largest part of the nasal cavity is respiratory region, also called conchae, is the cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, 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.[16] Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also has fine projections, called cilia.[38]

**Olfactory Region**

Location of olfactory region is at the roof of the nasal cavity and extends a short way down the septum and lateral wall. Its neuro-epithelium is the only part of the CNS that is directly exposed to the external environment. Similarly to the respiratory epithelium, the olfactory one is also pseudo stratified but contains specialized olfactory receptor cells important for smell perception.[40, 41] Olfactory mucosal cells are given in Fig. 2.

**Mucus Membrane of Nose and Its Composition**

The nasal mucus layer is only 5 µm thick and it is organized in two distinct layers: an external, viscous and dense, and an internal fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products.[38] The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 to 6.7 in children.[42]

The mucus secretion gives immune protection against inhaled bacteria and viruses. It also performs a number of physiological functions.

(1) It covers the mucosa physically and enzymatically protects it.
(2) The mucus has water holding capacity.
(3) It exhibits surface electrical activity.
(4) It permits efficient heat transfer.
(5) It acts as an adhesive and transports particulate matter towards the nasopharynx.[43]

**Epithelial Cells**

Basically there are two functions of these cells,

1. Provide a physical barrier to the invasion of infectious microorganisms and allergic particles;
2. Work in conjunction with mucus glands and cilia to secrete and remove mucus and foreign particles from the nasal cavity.[44] Types of epithelial cells are given in Fig. 3.

**Blood Supply to Nasal Cavity**

Vasculature of the nasal cavity is richly supplied with blood to fulfill the basic functions such as heating and humidification, olfaction, mucociliary clearance and immunological functions. The nasal vascular bed is so designed that rapid exchange of fluid and dissolved excipients between blood vessels and nasal tissue can be done easily. Blood supply comes from branches of both the internal and external carotid artery, including branches of the facial artery and maxillary artery.[31]

The capillary flow in the nasal mucosa was reported to be 0.5 ml/g/min.

- Sphenopalatine artery a branch of maxillary artery.
- Anterior ethmoidal artery a branch of ophthalmic artery.
- Branches of the facial artery supplying the vestibule of the nasal cavity

**Mechanism of Nasal Absorption**

The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin; it has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.).[45]

Fast rate of nasal absorption is lipophilicity dependant. Slower rate which is sensitive to the variation in molecular weight.[46] Small unchanged particles easily pass through this layer. Mechanisms for absorption through the nasal mucosa include paracellular transport via movement between cell and transcellular or simple diffusion across the membrane.[47] Drug transport pathways are shown in Fig. 4.

**a) First Mechanism**

It involves an aqueous route of transport, which is also known as the paracellular route but slow and passive. There is an inverse log log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 Daltons having drug shows poor bioavailability.[29]

**b) Second Mechanism**

It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membrane by an active transport route via carrier-mediated means or transport through the opening of tight junctions.[2] For examples: chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport.[48] Water soluble compounds such as Sodium chromoglycolate absorption based on diffusion through aqueous pores. Transport of Insulin involves passive diffusion where as transport of aminoacids involves active diffusion.[46]

**c) Carrier-Mediated Processes**

Active transport mechanisms for di and tripeptides, as well as L-amino acids, have been demonstrated in the nasal epithelium.

**d) Endocytic Processes**

Most compounds of interest for nasal delivery have a molecular weight more than of 1,000 Da and these were thought to cross the cells endocytically.[49]

**PATHWAYS**

The main transport pathway is

Olfactory epithelium → CNS → Peripheral circulation → Nasal absorption.

The process of drug transport across the nasal membrane involves either the diffusion of drug molecule through the pore channels in the nasal mucosa (or) participation of some non passive pathways before they reaches into the blood stream.[50] Possible pathways for absorption of drugs in Table 2.

**DISTRIBUTION AND DEPOSITION**

The drug distribution in the nasal cavity is one of the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could affect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation, it enhances the absorption of the drug and the posterior chamber of nasal cavity is used for the deposition of dosage form; it is eliminated by the mucociliary clearance process and hence shows low bioavailability.[56] The site of disposition and distribution of the dosage forms are mainly depends on delivery device, mode of administration, physicochemical properties of drug molecule.

**BARRIERS TO NASAL ABSORPTION**

Nasal drug delivery system is considered has a profitable route for the formulation scientist because it has easy and simple formulation strategies. Intra-nasally administered drug products therapeutic efficacy and toxicities are influenced by number of factors.[57]

Following factors are the barriers to the absorption of drugs through nasal cavity.

i) **Low Bioavailability** Bioavailability of polar drugs is generally low, about 10% for low molecular weight drugs and not above 1% for peptides such as calcitonin and insulin.[58] The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability.[59] Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. The pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after an intravenous injection and bioavailability approaching

100%.[60] Drugs can cross the epithelial cell membrane either by the transcellular route exploiting simple concentration gradients, by receptor mediated or vesicular transport mechanisms, or by the paracellular route through the tight junctions between the cells.

Polar drugs with molecular weights below 1000 Da will generally pass the membrane using the latter route. Although tight junctions are dynamic structures and can open and close to a certain degree when needed, the mean size of these channels is of the order of less than 10 Å and the transport of larger molecules is considerably more limited.[61]Larger peptides and proteins have been shown to be able to pass the nasal membrane using an endocytotic transport process but only in low amounts.[62] Nasal absorption of such polar drugs can be greatly improved by co-administration of absorption enhancing agents.[59]

ii) **Mucocilliary Clearence** The drugs administered by nasal route are subjected to fast clearance from the nasal cavity owing to mucociliary clearance mechanism is another factor of importance for low membrane transport. This is especially 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.[63, 64]

It has further been suggested that the deposition of a formulation in the anterior part of the nasal cavity can decrease clearance and promote absorption as compared to deposition further back in the nasal cavity.[64] Most nasal sprays of various makes have been shown to deliver the formulation to a limited area in the anterior part of the nasal cavity as opposed to nasal drops which will be delivered to a larger area further back in the nasal cavity. The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance. The clearance may also be reduced by depositing the formulation in the anterior, less ciliated part of the nasal cavity thus leading to improved absorption.[63, 64]

iii) **Enzymatic Degradation** Another contributing (but normally considered less important) factor to the low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic degradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier. These sites both contain exo-peptidases such as mono- and di amino peptidases that can cleave peptides at their N and C termini and endo-peptidases such as serine and cysteine, which can attack internal peptide bonds.[65] The use of enzyme inhibitors and/or saturation of enzymes may be the approaches to overcome this barrier.[66]

**Pharmacokinetics and Bioavailability**

The bioavailability of a drug after intranasal administration may be expressed in terms of the absolute nasal absorption *Bn* determined from the area under the plasma concentration versus time curve following the intravenous (IV) and intranasal (IN) dose.

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

Two types of kinetics profiles involved in transnasal permeation of drug

- Zero- order transnasal permeation kinetics
- First order transnasal permeation kinetics

**Zero Order Transnasal Permeation Kinetics[46]**

When a drug undergoes zero order kinetics when it administered as transnasal delivery system i.e. for example a controlled delivery of a drug at a constant rate of absorption, the plasma profile of the drug is explained by

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

Here

$K_o$ – Absorption rate constant

$K_e$ – Overall rate constant

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

Then the plasma concentration may be expressed as

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

$C_L$ – Total body clearance

**First Order Transnasal Permeation Kinetics**

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

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

Ka – 1st order rate constant
F a – Fraction of dose absorbed
XIN – Amount of dose administered through intranasal route.
The plasma concentration is expressed as

$$CP = F\,a\,X\,o\,IN\,Ka/\,V\,d\,(Ka-\,K\,e)\,(e^{-kat} - e^{-kat})$$

X o IN – Initial drug dose delivered at zero time
V d – Volume of distribution.

**Factors Influencing Nasal Drug Absorption[20]**

Several factors affect the systemic bioavailability of drugs which are administered through the nasal route. The factors affecting are: the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drug delivery systems. These factors play key role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration.
The factors influencing nasal drug absorption are described as follows

**Physicochemical Properties of Drugs [37, 31]**

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

**Formulation Factors**

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

**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 Drug**
**Molecular Weight and Size**

The molecular size of the drug influence absorption of the drug through the nasal route**.** The lipophilic drugs have direct relationship between the MW and drug permeation whereas water- soluble compounds depict an inverse relationship. The rate of permeation is highly sensitive to molecular size for compounds with MW ≥ 300 Daltons.[67] For compounds 1 kDa; bioavailability can be directly predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug do not significantly affect permeation of drug less than 300 Da, which will mostly permeate through aqueous channels of the membrane. By contrast, for compounds with MW 300 Da rate of permeation is highly sensitive.[38]

**Solubility**

Major Factor in determining absorption of drug through biological membranes is drug solubility. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Lipophilic drugs have less solubility in the aqueous secretions. Water soluble drugs are absorbed by passive diffusion and lipophilic drugs via active transport depending on their solubility.[68]

**Lipophilicity**

The hydrophilic and lipophilic nature of the drug also affects the process of absorption. By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, it appears that these mucosae are primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes.[69, 70] Systemic bioavailability of many drugs is decreased due to excess hydrophilicity in such cases prodrug approach is beneficial.[38] Lipophilic drugs like naloxone, buprenorphine, testosterone and 17α-ethinyl-oestradiol are almost completely absorbed when administered through intranasal route.[69, 70]

**pKa and Partition Coefficient**

As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same fact is true in the case of nasal absorption. There is constant relationship between pKa and nasal

absorption of these drugs. With an increase in lipophilicity or the partition coefficient of the drugs its concentration in biological tissues increases. The absorption rate of aminopyrine increased with the increase in pH and was found to fit well to the theoretical profile. Major factor governing nasal absorption is partition coefficient.[71]

**Polymorphism**

Polymorphism is an important parameter in the nasal drug product development which is administered in particulate form. Polymorphism is known to affect dissolution of drugs and their absorption through biological membrane. This factor should be carefully considered in the dosage form development for the nasal delivery**.**[72]

**Chemical State of Drug**

Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. Chemically alter the drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated.[72]

**Physical State of Drug**

Particle size and morphology of drug are two main important properties for particulate nasal drug products. These both parameters should be controlled to obtain suitable drug dissolution properties in the nostrils. Too fine particles below 5 microns should be avoided because it may get inhaled in lungs. Generally, particles in the 5–10 micron range are deposited in the nostrils.[72]

**Formulation Factors**

**pH of the Formulation**

Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption.[73] The pH of the formulation and nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria. pH of the nasal surface is 7.39 and the pH of nasal secretions is 5.5–6.5 in adults and 5.0–6.7 in infants and children.[37]

**Concentration Gradient**

Concentration gradient plays very important role in the absorption / permeation process of drug through the nasal membrane due to nasal mucosal damage. Examples for this are nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. Another is absorption of salicylic acid was found to decline with concentration. This decline is likely due to permanent nasal mucosa damage.[74]

**Buffer Capacity**

Nasal formulations are generally administered in small volumes ranging from 25 to 200µL. Hence, nasal secretions may alter the pH of the administrated dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.[73]

**Osmolarity**

Formulation tonicity substantially affect the nasal mucosa, an isotonic formulation is preferred. Some scientist studied the effects of formulation osmolarity, on the nasal absorption of secretin in rats. They found that all cells of the nasal mucosa were affected by the concentration of sodium chloride in the formulation and the absorption reached a maximum at a 0.462 M sodium chloride concentration. At this concentration shrinkage of epithelial cells was observed. Hence tonicity is also having impact on drug absorption.[75]

**Volume of Solution Applied and Drug Concentration**

There is no constant relationship between volume of administration and extent of absorption. Clement studied the effect of three nasal spray concentrations of cetrizine on the clinical efficacy. The results showed that 16.7%, 30.8%, 42.9%, and 26.7% of drugs the patients experienced appeared to improve with the drug concentration up to only 0.125%. At the higher concentration, 0.250%, the efficacy declined.[76] The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 200µL/ nostril have been suggested for the following reasons:

- To avoid irritation of nasal mucosa
- To allow the drug to be available in unionized form for absorption
- To prevent growth of pathogenic bacteria in the nasal passage

- To maintain functionality of excipients such as preservatives
- To sustain normal physiological ciliary movement.[73]

**Gelling / Viscosity Building Agents or Gel Forming Carriers**

It has been studied that increase in solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparation.[77] Contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation.[38] A drug carrier such as hydroxypropyl cellulose is effective for improving the absorption of low molecular weight drugs but does not produce the same effect for high molecular weight peptides.[78]

**Solubilizers**

Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins such as HP-β-cyclodextrin that serves as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers.[59]

**Preservatives**

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations. It has been shown that mercury containing preservatives have a fast and irreversible effect on ciliary movement and should not be used in the nasal systems.[79]

**Antioxidants**

Usually, antioxidants do not affect drug absorption or cause nasal irritation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxyl toluene and tocopherol.[59]

**Humectants**

Many allergic and chronic diseases are often connected with crusts and drying of mucous membrane. Therefore humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and are not likely to affect drug absorption. Common examples include glycerin, sorbitol and mannitol.[59]

**Role of Absorption Enhancers**

Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation by amino peptidases. Osmolarity and pH may accelerate the enhancing effect. Absorption enhancers improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal blood flow, decreasing mucus viscosity, and enzyme inhibition.[59]

**Biological Factors**

**Structural Features**

There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharnyx. These structures and the type of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increase the permeation of compounds.[80]

**Biochemical Changes**

Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect. Metabolism of nasal decongestants, alcohols, nicotine and cocaine is due to cytochrome p450 dependent monoxygenase system. Protease and peptidase were responsible for the presystemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin. To overcome these degradations various approaches have been used. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin.[81]

**Physiological Factors**

Blood supply and neuronal regulation: Nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively.[82] Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.[38]

**Nasal Secretions**

Nasal secretions are produced by anterior serous and seromucus glands. Mucus production is approximately 1.5–2 l ml daily. The permeability of drug through the nasal mucosa is affected by the following mechanisms[83]

1. **Viscosity of Nasal Secretion**
   The viscous surface layer will inhibit the ciliary beating if the solution layer of mucus is too thin and mucociliary clearance is impaired if solution layer is too thick, because contact with cilia is lost. Permeation of the drug is affected due to impairment of mucociliary clearence by altering the time of contact of drug and mucosa.
2. **Solubility of Drug in Nasal Secretions**
   For permeation of drug solublisation is necessary. A drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions.
3. **Diurnal Variation**
   Nasal secretions are also affected by circadian rhythm. Permeation of drug is altered at night due to secretions and clearance rates are reduced. Chronokinetics dictate the pattern and rate of permeation in such cases.
4. **pH of Nasal Cavity**
   variation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug is greater if the nasal pH is lower than pKa of drug because under such conditions the penetrant molecules exist as unionized species. Increase or decrease in the permeation of drug is observed because ionization is affected by change in pH of mucus, depending on the nature of the drug. pH of formulation should be between 4.5 to 6.5 for better absorption and should also have good buffering capacity.

**Pathological Conditions**

Mucociliary dysfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis, and drug permeation is affected by this[38].

**Environmental pH Conditions**

The environmental pH plays an important role in the efficiency of nasal drug absorption. Small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form. However, at pH values where these compounds are partially ionized, substantial absorption was found. This means that the nonionised lipophilic form crosses the nasal epithelial barrier via transcellular route, whereas the more hydrophilic ionized form passes through the aqueous paracellular route.[84] Moderate reduction in the rate of MCC occurs at the temperature of 24°C, it has been predicted that a linear increase in ciliary beat frequency occurs with increase in temperature.[38]

**Mucociliary Clearance and Ciliary Beating**

Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC because mucociliary clearance is the normal defense mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane because of reduced MCC; whereas, increased MCC decreases drug permeation.[38] The motor of the MCC and the mucus transport rate is 6 mm/min.

**Membrane Permeability**

Nasal membrane permeability is the most important factor, which affects the absorption of the drug through the nasal route. The water soluble drugs particularly large molecular weight drugs like peptides and proteins are having the low membrane permeability. So these compounds are mainly absorbed through the endocytotic transport process in low amounts.[62] Water-soluble high molecular weight drugs cross the nasal mucosa mainly by passive diffusion through the aqueous pores (i.e. tight junctions).

**Strategies to Improve Nasal Absorption[85]**

There are many barriers present in nasal cavity which interfere with absorption of various drugs. There are some methods which have been successfully used for the improvement of nasal drug absorption.

1. By improving the nasal residence time
2. By modifying the drug structure to change physicochemical properties.

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

bioavailability of the formulations. Several methods have been used to facilitate the nasal absorption of drugs includes.[20]

**1. Improving the Nasal Residence Time**

The nasal residence time can be improved by using nasal enzyme inhibitors. Nasal metabolism of drugs can be prevented by using the enzyme inhibitors.[86] Various kinds of enzyme inhibitors are used to minimize metabolism of drug in nasal cavity.[85] The permeation enhancers like salts and fusidic acid derivatives also show enzyme inhibition activity to increase the absorption and bioavailability of the drug.[87]The other enzyme inhibitors commonly used for the enzymatic activity are tripsin, aprotinin, borovaline, amastatin, bestatin and boroleucin inhibitors.

- **Permeation enhancers** The permeation enhancers are mainly used for the enhancement of absorption of the active medicament. Generally, the permeation enhancers act *via* one of the following mechanisms:
  1. Inhibiton of enzyme activity;
  2. Reduction of mucus viscosity or elasticity;
  3. Decrease in mucociliary clearance;
  4. Opening tight junctions; and
  5. Solubilizing or stabilizing the drug.

The mechanism of action of penetration enhancer is increasing the rate at which drug passes through the nasal mucosa. Many enhancers act by altering the structure of epithelial cells in some way, but they should accomplish this while causing no damage or permanent change to nasal mucosa.

**An ideal permeation enhancer**

1. Should lead to an effective increase in the absorption of the drug.
2. Should not cause permanent damage or alteration to the tissues
3. Should be non irritant and nontoxic.
4. Should be effective in small quantity
5. The enhancing effect should occur when absorption is required
6. The effect should be temporary and reversible
7. Should be compatible with other excipients.

Various types of penetration enhancers have been evaluated for organic drugs including surfactants, bile salts, fusidic acid derivatives, chelators, fatty acid salts, phospholipids, glycyrrhetenic acid derivatives, cyclodextrins and glycols.e.g.[89]

- o Surfactants**-** Polyozyethylene-9-lauryl ether (Laureth- 9), Saponin
- o Bile salts **-** Trihydroxy salts (glycol- and taurocholate),
- o Fusidic acid derivatives - STDHF
- o Chelators **-** Salicylates, EDTA
- o Fatty acid salts - Oleic acid, Caprylate (C8), Caprate (C10), Laurate (C12)
- o Phospholipids - Lysophosphatidylcholine (lyso-PC), Didecanoyl – PC
- o Glycyrrhetinic acid derivates **-** Carbenozolone**,** Glycyrrhizinate
- o Cyclodextrins **-** α, ß, and γ-cyclodextrins and their derivatives
- o Glycols **-** N- glycofurols and N-ethylene glycols.

**2. Structural Modification**

Modification of drug structure can be done without changing the pharmacological activity for improvement of nasal absorption.[85] 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 are favorable to improve the nasal absorption. Example, chemical modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability than salmon calcitonin.[88]

- **Prodrug Approach**
  Prodrug approach is mainly meant for optimizing favorable physicochemical properties such as solubility, taste, odor, stability, etc. Prodrug is usually referred as promoiety, it is to cover the undesired functional groups with another functional groups. This prodrug approach is mainly for improving the nasal bioavailability especially for the proteins and peptides to enhance the membrane permeability along with increased enzymatic stability.[11] The prodrug undergoes enzymatic transformation to release the active medicament, when it crosses the enzymatic and membrane barrier. The absorption of peptides like angiotensin II, bradykinin, caulein, carnosine, enkephalin, vasopressin and calcitonin are improved by prepared into enamine derivatives, these agents showed absorption enhancement with prodrug approach.[20]

**3. Particulate Drug Delivery**

Particle design is an increasingly important role in absorption enhancement.[20] Carriers are

used for the encapsulation of drug which prevent exposure of a drug to nasal environment and improve the retention capacity in nasal cavity. Some examples of carriers may include microspheres, liposomes, nanoparticles and niosomes.[85] The properties of these can be varied to maximize therapeutic efficacy. Overall, 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.[20]

- Microspheres mainly increase the absorption and bioavailability by adhering to the nasal mucosa and increase the nasal residence time of drug.[90] The microspheres prepared by using polymers like dextran, chitosan, biodegradable starch successfully improved 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 as liposomes. Cationic liposomes are having good permeation capacity than negatively charged anionic liposomes.[91]

**4. Bioadhesive Polymer**

To improve the nasal residence and absorption of the drug bioadhesive polymers are used. They improve the retention time of the drug inside the nasal cavity by making an adhesive force between formulation and nasal mucosa, which leads to minimize the mucociliary clearance of formulation.

**5. In situ Gel**

These are the formulations which get converted into gel upon instillation into nasal cavity by the influence of stimuli includes temperature, pH and ionic concentration. Consistency of the gel is thick which makes the formulation difficult to drain by the influence of ciliate movement.[85]

**Nasal Mucoadhesion[92]**

The process of mucoadhesion following nasal administration relates to the interaction between the mucoadhesive polymer and the mucus secreted by the sub-mucosal glands. The sequential events that occur during the mucoadhesion include the proper wetting and swelling of the polymer, and intimate contact between the polymer and the nasal mucosa Fig. 5. Then, the swelled mucoadhesive polymer penetrates into the tissue crevices followed by the interpenetration between the polymer chains and protein chains of the mucus. To obtain sufficient absorption of drugs, first the formulation should spread well on the nasal mucosa. Therefore, the spreadability is very important for the liquid mucoadhesive formulation, so do the flowability and wettability for the solid mucoadhesive formulation.

Hydration of the polymer (swelling) plays a very important role in mucoadhesion, through which the polymer chains are liberated and interact with the biological tissue Fig. 6. During hydration, there is a dissociation of hydrogen bonds of the polymer chains. When the polymer–water interaction becomes greater than the polymer–polymer interaction, adequate free polymer chains will be available for interaction between the polymer and biological tissue.

There is a critical degree of hydration required for optimum mucoadhesion. The incomplete hydration due to the lack of the water leads to incomplete liberation of the polymer chains. On the other hand, an excessive amount of water will weaken the mucoadhesive bonds by over diluting the polymer solution. The polymer chains penetrating into the tissue crevices can hold back the ciliary movement, which will increase the retention time of the drugs in the nasal cavity. Furthermore, the existence of the mucoadhesive carrier also reduces the contact between the drugs and the enzymes existing in the mucosa. These both can enhance the intranasal absorption of hydrophilic drugs.Theories of mucoadhesion is given in Table 4.

**Reason for Development of Nasal Delivery [73]**

Nasal drug delivery is a useful delivery method for drugs that are active in low doses and show no or minimal oral bioavailability. The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible and suitable for self medication. Currently, two classes of nasally delivered therapeutics are in the market. The first one comprises low molecular weight and hydrophobic drugs for the treatment of the nasal mucosa and sinus, including decongestants, topical steroids, antibiotics and other (OTC) products.

The second class encompasses a few drugs, which have sufficient nasal absorption for displaying systemic effects. Important candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, due to their instability in gastrointestinal tract, poor absorption

properties, and their rapid and extensive biotransformation.

**Ideal Characteristics of Nasal Drug Delivery System [72, 38]**

1. The nasal route provides appropriate aqueous solubility approximately 25–150 ml volume of formulation administration per nostril.
2. Better nasal absorption properties.
3. Rapid onset of action.

**Profile of An 'Ideal' Drug Candidate For Nasal Delivery [72]**

Drugs for trans mucosal nasal drug delivery given in Table 4.

An ideal nasal drug candidate should possess the following attributes:

- Appropriate aqueous solubility to provide the desired dose in a 25–150 µl volume of formulation administration per nostril.
- Non irritant.
- Non toxic
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose.
- Non toxic
- Non odors
- Suitable stability characteristics.

**Types of Nasal Drug Delivery** explained in Fig. 7.

**Polymers Used In Nasal Drug Delivery [92]**

**Hydrophilic Polymers**

Contains carboxylic group and possess excellent mucoadhesive properties. They are,

- PVP(Poly vinyl pyrrolidine)
- MC(Methyl cellulose)
- SCMC(Sodium carboxy metyhyl cellulose)
- HPC(Hydroxyl propyl cellulose)

**Hydrogels**

These swell when in contact with water and adhere to the mucus membrane. These are further classified according to their charge

- Anionic polymers- carbopol, polyacrylates
- Cationic polymers- chitosan
- Neutral/ non ionic polymers- Eudragit analogues.

**Cellulose Derivatives**

There are many pharmaceutical grade derivatives of cellulose widely used in different administration routes. Several cellulose derivatives have proved to be effective on enhancing the intranasal absorption of drugs, including soluble cellulose derivatives such as HPMC, HPC, MC, CMC, and insoluble cellulose derivatives such as ethylcellulose and MCC. Cellulose derivatives can markedly prolong the residence time of drugs in the nasal cavity due to their desirable mucoadhesive property.[115] Additionally, due to their high viscosity following hydration in the nasal cavity, the celluloses can sustain the release of drugs.[101]

For these reasons, using celluloses as absorption enhancer can lead to improved intranasal absorption and increased bioavailability. Many references show that the celluloses are effective on increasing the intranasal bioavailability of small hydrophobic as well as hydrophilic macromolecular drugs. For example, drug (apomorphine) administered nasally with CMC, can obtain a relative bioavailability of 102% compared with subcutaneous injection in rabbits.[93]

Another study reported that an absolute bioavailability up to 90.77% could be achieved for ketorolac tromethamine administered with MCC.[116] The peptide drugs, leuprolide and FD-4, when dosed with MCC/HPC through nasal route, reached an absolute bioavailability of 34.9% and 35.5% in rabbits, respectively.[110]

Sometimes, combination of the celluloses with other absorption enhancer would obtain the better effectiveness than using the polymer alone.[117] The intranasal absolute bioavailability of ciprofloxacin in rabbits using MC and HEC alone as enhancer is only 18.2% and 19.46%, respectively.[118] When combining with the tween 80, the bioavailability increased to 22.35% and 25.39%, respectively. In another study the intranasal delivery of dopamine, the combination of the HPC and azone led to an absolute bioavailability of almost 100%, while it was only 25% for HPC alone.[119]

Examples for some nasal drug delivery systems where cellulose derivatives were employed: Apomorphine with CMC as powder form, ketorolac with MCC as spray, dopamine with HPC as liquid form and metaclopromaide with HPC as gel form.

**Polyacrylates**

Polyacrylates have been investigated very frequently in many drug administration routes, like nasal drug delivery systems, due to their excellent muco-adhesive and gel-forming capability. Among the pharmaceutical polyacrylates, carbomers, and polycarbophil, which differ in the cross-linking condition and viscosity, are widely used in the nasal mucoadhesive drug delivery systems.[118]

Polyacrylates, capable of attaching to mucosal surfaces, can offer the prospects of prolonging the residence time of drugs at the sites of drug absorption, and ensure intimate contact between the formulation and membrane surface. Studies by Ugwoke *et al*. in rabbits reported that the use of Carbopol 971P in nasal dosage form increases its residence time in the nasal cavity. The percentage of the formulations cleared from the nasal cavity at 3 hours was 24% for Carbopol 971P, while it was 70% for lactose. Sustained release of drugs can also be obtained by using polyacrylates in nasal formulation, which results in a more stable blood concentration-time curve. 93,120.

Another research by Ugwoke *et al*. showed that the $t_{max}$ of the Carbopol 971P-containing formulation of apomorphine was 52.21 minutes, which represented a 5-fold improvement compared with that of the lactose-containing formulation, while the Cmax of the Carbopol 971P-containing formulation was 330.2 ng/ml, lower than that of the lactose-containing formulation, which was 450.7 ng/ml.[93, 121]

Besides the mucoadhesion capability, polyacrylates may also temporarily open the tight junctions between the epithelial cells during the swelling progress in the nasal cavity and improve the paracellular absorption of drugs.[122] An absolute bioavailability of 14.4% in rabbits was reported for intranasal insulin formulation containing Carbopol 974P.

Callens and Remon reported that the effect of Carbopol on the mucosa is negligible and reversible, no change of the epithelium barrier was observed even after a 4-week administration of Carbopol-based powder formulation in rabbits. Examples for some nasal drug delivery systems where polyacrylate derivatives were employed: Apomorphine with Carbopol 971P, Metadopramide with carbopool 981P/Dm B – CD and Metadopramide with carbopol934/HPC as powder form.

**Starch**

The starch is one of the most widely used mucoadhesive carrier for nasal drug delivery, which has been reported to be effective on improving the absorption of both small hydrophobic drugs and hydrophilic macromolecular drugs. Maize starch is the most preferred class for pharmaceutical purpose, among which the drum-dried waxy maize starch, due to its better bioadhesive property, has been considered as the best one compared with starch processed through other methods.[123]

Starch can be used as nasal drug carrier in the form of powder microspheres nanoparticles among which the DSM also known as SpherexR, is the most widely used and also the first example of mucoadhesive microparticulate nasal delivery system. These microspheres are prepared by an emulsion polymerization technique, in which the starch is cross-linked with epichlorohydrin and can incorporate molecules weighing less than 30 kDa [124] have observed that the half-life of clearance for DSM was prolonged to 240 minutes as compared with 15 minutes for the liquid and powder control formulations.[125]

Examples for some nasal drug delivery systems where starch and other carbohydrates derivatives were employed: apomorphine with DSM, gentamycin with DSM/STDHF and mercurials with DDMW as powder form.

**Chitosan**

Chitosan [2-amino-2-deoxy-(1→4)-β-d-glucopyranan] is a linear cationic polysaccharide which is obtained by a process of deacetylation from chitin, an abundant structural polysaccharide in shells of crustacea, such as lobsters, shrimps, and crabs. Due to the $NH_2$ group resultant from the deacetylation process, chitosan is insoluble at neutral and alkaline pH. However, it can form water-soluble salts with inorganic and organic acids including glutamic acid, hydrochloric acid, lactic acid, and acetic acid. Toxicity tests have revealed that the LD50 of chitosan in mice exceeds 16 g/kg (Paul and Garside, 2000). Because of its low cost, biodegradability, and biocompatibility, chitosan has been increasingly applied as pharmaceutical excipients in oral, ocular, nasal, implant, parenteral, and transdermal drug delivery.[114]

Chitosan and its derivatives have been shown to be active in enhancing the intranasal drug absorption due to their excellent mucoadhesive properties. It was also confirmed that coating micro- and nanoparticulates with chitosan could improve drug adsorption to mucosal surfaces.[126]

Soane *et al*. reported that chitosan microspheres and solutions resulted in three- and eight-fold longer clearance half-lives compared with sodium pertechnetate solution in sheep nasal cavity, respectively.[127, 128] In addition, many studies have proved that chitosan and its derivatives could transiently open the tight junctions between the cells and lead to the paracellular transport of drugs.[129]

Chung *et al*. have observed interpenetration of thermo-sensitive gels of insulin in nasal

delivery by cross linking of chitosan. The preparation shows sustained release of insulin and improved pharmacological efficiency.[130]

Chemical and biological properties of chitosan, such as mucoadhesion and ability in enhancing nasal absorption, are determined by the types of derivatives, degree of deacetylation, and molecular weight, because chitosan is only soluble in acidic environment in which the amino groups at the C-2 position are protonated. At neutral pH, most chitosan molecules will lose their charge and precipitate from solution.[130]

Recent studies have shown that only protonated, soluble chitosan can trigger the opening of tight junctions and thereby facilitate the paracellular transport of hydrophilic mannitol.[131] To improve the poor water solubility of chitosan, some derivatives were synthesized, such as trimethyl chitosan.[132]

Thanou *et al*. reported that the trimethyl chitosan was soluble and effective on enhancing intranasal absorption even at neutral pH.[133] N-trimethyl chitosan hydrochlorides are more mucoadhesive than unmodified chitosans and show a higher bioavailability *in vivo* compared with the unmodified chitosan.[134] Mei *et al*. reported that the permeation-enhancing effect of chitosan increased with increasing molecular weight up to Molecular weight 100.[135] Tengamnuay *et al*. suggested that chitosans should differ in their molecular weight by at least two-fold in order to have a clearly differentiating effect on the nasal absorption enhancement of a kyotorphin analogue.[136]

On the contrary, Zaki *et al*. found that there is no significant difference between the constants of intranasal absorption for metoclopramide HCl administered with chitosan high molecular weight (600 kDa) and low weight (150 kDa) even though they differ in molecular weight by four-fold. Due to the positive charge of chitosan in a weak acidic environment, it can also be applied to deliver the negatively charged DNA through nasal mucosa and protect them from nuclease degradation.[116]

Compared with viral vectors, this alternative vector markedly reduced the safety risks that result in high transfectability. Recently, many studies show that nasal immunization with chitosan plus inactive vaccine is a potentially effective, easily administered form of vaccination.[137] *Bordetella pertussis* filamentous hemagglutinin and recombinant pertussis toxin have shown to induce very strong systemic and mucosal immune reactions against the antigens when intranasally administrated with chitosan.[138]

Read *et al*. confirmed that the standard inactivated trivalent influenza vaccine administered intranasally in combination with chitosan glutamate (0.5%, w/w) could induce both systemic and local immune responses, and the results were not statistically different from those obtained following administration of the commercial influenza vaccine by the intramuscular route.

Bacon *et al*. have reported that chitosan solutions are able to enhance both the mucosal and systemic immune responses against influenza virus vaccines. Only in mice which received chitosan/vaccine formulation intranasally, high IgA titers in nasal washings could be found. This was not observed in mice receiving the antigen through subcutaneous injection.[139]

Examples for some nasal drug delivery systems where chitosan derivatives were employed: Tetramethyl pyrazosine, insulin and metaclopromaide with chitosan as liquid form.

**Mucoadhesive Polymers [140]**

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable systems, jointed by cross-interfacing agent. These polymers have ideal extremity to verify that they allow sufficient wetting by the mucus and ideal smoothness that allows the common adsorption and interpenetration of polymer and mucus to happen. Mucoadhesive polymers that adhere to the mucin-epithelial surface might be advantageously isolated into three wide classes:

1. Polymers that get to be sticky when put in water and owe their mucoadhesion to stickiness.
2. Polymers that follow through nonspecific, non-covalent communications that is basically electrostatic in nature (in spite of the fact that hydrogen and hydrophobic holding may be huge).
3. Polymers that tie to particular receptor site on tile surface toward oneself. Each of the three polymer sorts could be utilized for medication conveyance.

**Ideal Mucoadhesive Polymer Characteristics**

A mucoadhesion promoting agent or the polymer is added to the formulation which serves to promote the following of the dynamic pharmaceutical element to the mucosa. The agent can have such extra properties like swelling to promote the disintegration when in contact with the secretion. As under stood, that different physical and chemical compound trades can influence the polymer/mucus

adhesion, so as polymer should be precisely chosen on account of the accompanying properties.[141]

**Molecular Weight**
Polymer must have a high molecular weight upto 100.00 or more this is important to advertise the adhesiveness between the polymer and mucus.[141]

**Polymers-chain Length**
Polymers-chain length must be long enough to push the interpenetration and it should not be excessively long that diffusion turns into an issue.

**Thickness**
High thickness.

**Level of Cross Interfacing**
Level of cross interfacing it impacts bind versatility and imperviousness to disintegration. Exceedingly cross linked polymers swell in vicinity of water and hold their structure. Swelling favours controlled arrival of the medication and expands the polymer/mucus interpenetration. Yet as the cross interfacing expands, the chain portability diminishes which decreases the mucoadhesive quality.[142]

**Adaptability of Polymer Chain**
This pushes the interpenetration of the polymer inside the bodily fluid system.[143]

**Concentration of the Polymer**
An ideal optimization is required to promote the mucoadhesive quality. It depends in any case; on the solid dosage form the adhesive strength increases with increase in the polymer concentration. But in case of semi-solid dosage forms an optimum concentration essential beyond which the adhesive strength decreases.[144]

**Ideal Hydration**
Excessive hydration prompts diminished mucoadhesive quality because of structuring of slippery mucilage.[145-147]

**Ideal pH**
Mucoadhesion is ideal at low pH conditions however at pH conditions yet at higher pH values a change in the conformity happens into a pole like structure making them more accessible for entomb dispersion and interpenetration.[148] At exceptionally lifted pH values, emphatically charged polymers like chitosan structure polyelectrolyte edifices with mucus and display solid mucoadhesive strengths.

- High applied strength and initial contact time.
- Polymer should be nontoxic, economical, biocompatible ideally biodegradable.[149]

**bio-Adhesive polymer** [49]
**Bio-adhesives**
Bio-adhesives adhere to biological substrates such as mucus or tissue. Bioadhesives are proposed to influence drug bioavailability by: Decreasing the rate of clearance from the absorption site thereby increasing the time available for absorption. Increasing the local drug concentration at the site of adhesion/ absorption so, protect the drug from dilution and possible degradation by nasal secretions.

**Bio-adhesive Polymers**
Compound that is capable of interacting with biological material through interfacial forces and being retained on such material for prolonged periods of time is called as bioadhesive polymer. They are also called as mucoadhesive if biological material is mucus membrane. Bio adhesive polymers used in nasal drug delivery system Table 5.

**Formulation Development Research in Nasal Drug Delivery** [150, 4]
Over the counter nasal preparation are formulated as solution, to treat the nasal symptoms of allergic rhinitis and common cold. A simple drug solution is adequate for this purpose as it produces better dispersion over greater surface area. The nasal residence time of such formulation is short (3-20 min) and exhibit high inter-individual variability.
This route provides fast peak levels in circulation. Large number of drugs has been evaluated for systemic bioavailability after transnasal administration in experimental animal models. Transnasal administration of drugs in diverse dosage forms such as sprays, powders, and microspheres has been attempted for improved residence and bioavailability. The nasal delivery is receiving attention for management of postoperative pain; mucosal administration requires only a 1.1-1.5 time higher dose of fentanyl than i.v. dose. The nasal delivery of vaccines is a very attractive route of administration in terms of efficacy.

**Nasal Formulations** [151]
Designing of nasal formulation depends upon the therapeutic need of the particular drug molecule, duration of action and duration of

therapy. Both controlled release and conventional release drug delivery are possible through nasal route. Requirement of the pharmaceutical excipients depend upon the mode of drug delivery i.e. local or systemic drug delivery. Wide range of nasal formulations has been studied so far and these include,

1. Nasal drops
2. Nasal powders
3. Nasal sprays (solution/suspension)
4. Nasal particulate drug delivery system(Micro/nanoparticles, liposomes)
5. Nasal gel
6. Nasal ointments
7. Nasal micro emulsions.

**Excipients in Nasal Drug Delivery System** [38]

There are various type of excipients are used in the formulation of nasal drug delivery system. Polymer is one of the essential excipients are used in nasal formulations. e.g: Table 6.

**Liquid nasal Formulations**

Liquid preparations are the most widely used dosage forms for nasal administration of drugs. They are mainly based on aqueous state formulations. Their humidifying effect is convenient and useful, since

Many allergic and chronic diseases are often connected with crusts and drying of mucous membranes. Microbiological stability, irritation and allergic rhinitis are the major drawbacks associated with the water-based dosage forms because the required preservatives impair muco-ciliary function.[152] The reduced chemical stability of the dissolved drug substance and the short residence time of the formulation in the nasal cavity are major disadvantages of liquid formulations.[125, 153]

**Nasal Drops**

Nasal drops are one of the most simple and convenient delivery systems among all formulations.

The main disadvantage of this system is the lack of dose precision.[35, 2] It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays. Upon the instillation of one or more drops of drug solution either from a dropper with a flexible (rubber) teat or directly from a “squeezable” plastic container into the nasal cavity.

Nasal drops, if administered correctly deposit drug throughout the nasal cavity, which offers a larger effective area for immediate absorption than if the drug is delivered in form of a spray. Some drugs are deposited on the ciliated regions of the mucosa and is therefore immediately available for clearance.

A proportion of the dose actually deposits at the Nasopharnyx where it may be immediately swallowed and is therefore not available for nasal absorption. Ex: meclizine HCl.[49]

**Preparation Methods/Techniques** [154]

**Solutions**

The ingredients are weighed/ measured accurately. The ingredients are dissolved in about 3/4 of the quantity of Sterile Water for Injection and mixed well. The sufficient quantity of Sterile Water for Injection is added to the volume and mixed well. The pH, clarity and other quality control factors from a sample of the solution are determined. Filter through a sterile 0.2µ filter into a sterile nasal container. Packaged and labeled. If a large number are to be prepared, a random sample is selected and checked for sterility.

**Evaluation** [154]

The following test parameters are recommended for nasal drops drug products.

- Description
- Preservatives and Stabilizing Excipients Assay
- pH
- Isotonicity
- Viscosity
- Weight Loss (Stability)
- Leachable (Stability)
- Sterility
- Particulate Matter
- Microbial Limits
- Pump Delivery
- Spray Content Uniformity
- Spray Pattern and Plume Geometry
- Droplet Size Distribution
- Particle Size Distribution (Suspensions)
- Net Content

**Nasal Sprays**

Nasal sprays are available as squeeze bottles which would not be expected to give reproducible dosing. They are also available as metered dose devices which would be expected to give more reproducible dosing as a mechanical actuation delivers a predetermined volume to the patient. Thus the dose of drug received by the patient will be dependent on the concentration of drug in the formulation. Nasal sprays tend to deposit at their impaction site in the anterior, non-ciliated regions of the nasal cavity, where air-flow associated with inspiration is high and mucociliary clearance is slow or erratic. Thus a

drug moiety depositing in this region is cleared slowly and is transported over a large area en-route to the pharynx. These factors promote drug absorption. Ex: atropine, penicillin, hyoscine etc.[49] Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose anywhere from 25 -200 µL.[35, 2] The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.[49]

**Evaluation**

Evaluation of nasal spray formulations as same as in nasal drops products.

**Nasal Emulsions, Micro Emulsions**

Intranasal emulsions have not been studied as extensively as other liquid nasal delivery systems.

Nasal emulsions offer the advantages for local application mainly due to the viscosity. The degradation of drug is less in emulsion form.[35, 2]

**Nasal Suspensions**

Suspensions for nasal administration are prepared by suspending the micronized drug in a liquid diluent or carrier suitable for application to the nasal mucosa. The suspension form of nasal formulation gives a better insulin uptake and blood glucose reduction when compared with that of the solution formulation.[92]

**Suspensions Preparation Technique[36]**

The ingredients are weighed/ measured accurately. The ingredients are dissolved in about 3/4 of the quantity of Sterile Water for Injection and mixed well. The sufficient quantity of Sterile Water for Injection is added to the volume and mixed well. The pH, clarity and other quality control factors from a sample of the solution are determined. Packaged in a suitable container for autoclaving and labeled. If a large number are to be prepared, select a random sample checked for sterility.

**Powder Dosage Forms**

**Nasal Powders**

Powder dosage forms of drugs for nasal administration offer several advantages over liquid formulations. In the powder form, the chemical stability of the drug is increased, a preservative in the formulation is not required, and it is possible to administer larger doses of drugs**.** Polymer-based powder formulations show no adhesion until their absorption on the nasal mucosa occurs. This allows easy application to the nasal cavity by metered dose insufflations even if the polymer is highly mucoadhesive.[92]

Administration of nasal powders may increase patient non-compliance, especially if the smell and taste of the delivered drug is unacceptable. After getting in contact with the nasal mucosa, polymer-based powders are believed to form a viscous gel following absorption of water from the nasal mucus. It is possible to administer larger doses of drugs. Powder form is suitable for number of non-peptide drugs and is well suited for peptide drugs.[92] However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients.[35, 2]

**Dry Powders**

Dry powders are less frequently used in nasal drug delivery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation and no need for freeze storage. Compared to solutions, the administration of powders could result in a prolonged contact with the nasal mucosa.[155] For these reasons, the dried powder is the most commonly studied formulation for the nasal drug delivery, including small hydrophobic drugs, peptide drugs, and vaccine.[92]

**Semi-Solid Dosage Forms**

Semi-solid systems, for example gels, ointments and liquid systems containing polymers that gel at particular pH changes are usually employed for designing the nasal drug delivery systems.[35, 2]

**Ointments Preparation Technique**

The ingredients are weighed/ measured accurately. The ingredients are sterilized by a suitable method. Each of the ingredients are Mixed with the sterile vehicle. The quality control factors from a sample of the product is determined, Packaged and labeled. If a large number are to be prepared, a random sample is selected and checked for sterility.

**Nasal Gels**

Nasal gels are high viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there was not much interest in this system. The advantages of a nasal gel include the reduction of 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 by using soothing/emollient excipients and target delivery to mucosa for better absorption.[156]

The deposition of the gel in the nasal cavity depends on the mode of administration, because due to its viscosity the formulation has poor spreading abilities. Without 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.

**Gels Preparation Technique**

The ingredients are weighed/ measured accurately. The ingredients are dissolved in about 3/4 of the quantity of Sterile Water for Injection and mix well. Filter through a sterile 0.2 µ filter into a sterile container. The gelling agent (previously sterilized) s added and mixed well. Sufficient Sterile Water for Injection is added to volume/weight and mixed well. The pH, clarity and other quality control factors from a sample of the gel is determined. Packed and labeled (Sterile 1 ml syringes preloaded with individual doses work well). If a large number are to be prepared, a random sample is selected and checked for sterility.

**Evaluation** [157]

- Clarity
- Viscosity
- Texture analysis
- Drug content
- Gel strength
- Sol-gel transition temperature and gelling time
- Drug polymer interaction study and thermal analysis
- Gelling capacity
- Isotonicity evaluation
- Sterility testing
- Accelerated stability studies
- In vitro drug release studies

**Nasal Particulate Drug Delivery System**

Nasal particulate systems using mucoadhesive polymers as carriers include microparticle/sphere and nanoparticle. Particulate drug carrier systems administered through nasal mucosa may protect the drug from enzymatic degradation, increase the drug dissolution rate, intensify the contact of the formulation with the mucosa, enhance the uptake by the epithelium, and act as a controlled release system resulting in prolonged blood concentrations.

The positively charged polymers such as chitosan and aminated gelatin are most frequently used in nasal drug particulate system, because of their hydrogel nature which leads to opening of the tight junctions and their intimate contact with the negatively charged mucosa membrane.[92]

**Nanoparticles**

Nanoparticles are solid colloidal particles with diameters raging from 1-1000 nm. They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached.

Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4Å.[35, 2] Nanoparticles cross the mucosal epithelium better than microspheres. Microparticles smaller than 10 µm administered intranasally are believed to be taken up by the M-cells overlaying the NALT and transported to submucosal layers. However, in case of the nanoparticles, besides the M-cell-associated phagocytosis, the epithelial cells are also involved in the transport of nanoparticles by internalization. Association of vaccines to the nanoparticulate systems have shown to enhance the antigen uptake by nasal lymphoid tissues.[92]

**Liposomes**

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

Liposomes protect the entrapped peptides from enzymatic degradation and mucosal membrane disruption.[35, 2] Amphiphilic drugs can be adsorbed at the head group region of the bilayers.[158] Liposomes have been investigated as carriers of various pharmacologically active agents such as antineoplastic, antimicrobial drugs, chelating agents, steroids, vaccines, and genetic materials[159] Table 7.

**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 Table 8.

**General Method of Preparation of Microspheres[169]**

The microspheres can be prepared by using any of the several techniques enlisted following. But the choice of the technique mainly depends on the nature of the polymer used for the intended use and the duration of therapy.

- Single emulsion technique
- Polymerization techniques
- Interfacial polymerization
- Phase separation/coacervation techniques
- Spray drying and spray congealing
- Solvent evaporation
- Chemical and thermal cross-linking.

**Bio-Adhesive Formulations[49]**

**a) Bio-adhesive Solutions/Suspensions**

Many viscosity enhancers are also considered to be bio-adhesive and putative bio adhesive polymer gels, including methyl-cellulose, sodium carboxy methyl cellulose, chitosan, carbopol 934p and pluronic F127, have been shown to decrease the rate of mucociliary clearance. By reducing or abolishing ciliary motility the rate of clearance of the drug from the nasal cavity is reduced. Some bio-adhesives, such as carbomers have also been shown to complex with mucus, increasing the viscoelasticity.

**b) Dry Powder Bio-adhesives**

A slightly different approach is to deliver the active drug in a dry powder carrier system Ex: microcrystalline cellulose, hydroxyethyl starch, cross linked dextran, microcrystalline chitosan, carbomer, pectin, or alginic acid. The polymer absorbs water upon contact with the nasal mucosa and swells to become a viscous gel, often demonstrating bio-adhesive properties. Such systems can remain in the nasal cavity for as long as six hours.

**c) Colloidal Bio-adhesives**

Bio-adhesive micro-spheres composed from a variety of materials such as starch, carbomer, hyaluronan esters, and dextrin have been used to prolong the retention time of the drug within the nasal cavity. The clearance half-life of micro-spheres can be in the order of 3-4 hours, in comparison with 15 min. for a simple solution. Ex: Gentamycin, insulin and Desmopressin.

**Delivery Systems for Intranasal Drug Administration**

There are several types of drug delivery system, which have been long used for the delivery of drug to nasal cavity, such as nasal spray, nasal drops, saturated cotton pledge, aerosol spray and insufflators.

Lists of drugs that have been administered intransally for systemic medication and type of drug delivery devices used Table 9.

**Liquid Nasal Drug Delivery Devices**

The several types of devices available for administration of liquid nasal formulations are described below.

**Instillation and Rhinyle Catheter**

Catheters are used to deliver the drops to a specified region of nasal cavity easily. Place the formulations placed in the tube and one end of the tube was positioned in the nose, and the solution is delivered into the nasal cavity by blowing through the other end by mouth.[170, 64] Dosing of catheters is determined by the filling prior to administration and accuracy of the system and this is mainly used for experimental studies only.

**Compressed Air Nebulizers**

Nebulizer is a device used to administer medication in the form of a mist inhaled into the lungs. The compressed air is filled into the device, so it is called compressed air nebulizers. The common technical principle for all nebulizers is to use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device.[171]

Nebulizers accept their medicine in the form of a liquid, which is often loaded into the device upon use. Corticosteroids and Bronchodilators such as salbutamol are often used, and sometimes in combination with ipratropium.[5] The reason these pharmaceuticals are inhaled instead of ingested is in order to target their effect to the respiratory tract, which speeds onset of action of the medicine and reduces side effects, compared to other alternative intake routes.

**Squeezed Bottle**

Squeezed nasal bottles are mainly used as delivery devices for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside.

Dose accuracy and deposition of liquids delivered via squeezed nasal bottles are strongly dependent on the mode of administration. The differences between vigorously and smoothly pressed applications influence the dose as well as the droplet size of the formulation. Thus the dose is hard to control. Therefore squeezed bottles with vasoconstrictors are not recommended to be used by children.[172]

**Metered-Dose Pump Sprays**

Most of the pharmaceutical nasal preparations in the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to alleviate cold or allergic symptoms such as nasal congestion. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand-operated pump mechanism. The three main types of devices available for local effect are: antihistamines, corticosteroids, and topical decongestants.

Metered dose pump sprays include 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. For solutions with higher viscosity, special pump and valve combinations are in the market.[20]

Examples of Liquid nasal devices are used for administration of drugs are given in Table 10.

**Powder Dosage Forms**

**Insufflators**

Insufflators are the devices to deliver the drug substance for inhalation; it can be constructed by using a straw or tube which contains the drug substance and sometimes it contains 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 a high coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsule.[170]

DPIs are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. DPIs are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non polar volatile propellant or in DPI that is fluidized when the patient inhales.[20]These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus. The medication is commonly held 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 their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough.[174]

**Pressurized MDIs**

A MDI is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, COPD and other respiratory diseases. The medication in a metered dose inhaler is most commonly 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).[5] The advantages 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 quickly ready for use.[174]

To use the inhaler the patient presses down on the top of the canister, with their thumb supporting the lower portion of the actuator. The propellant provides the force to generate 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 releases a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized

medication particles that are then inhaled.[173] Examples of Liquid nasal devices are used for administration of drugs are given in Table 11.

**Evaluation of Nasal Drug Formulations [177, 35]**

**In-Vitro Nasal Permeation Studies**

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

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

**In-Vivo Nasal Absorption Studies**

**Animal Models for Nasal Absorption Studies**

The animal models employed for nasal absorption studies can be of two types, viz., whole animal or *in -vivo* model and an isolated organ perfusion or *ex-vivo* model. These models are discussed in detail below ***In -vivo* Model**

- **Rat Model**
  The surgical preparation of rat for in vivo nasal absorption study is carried out as follows: The rat is anaesthetized by intra-peritoneal injection of sodium pentobarbital. An incision is made in the neck and the trachea is cannulated with a polyethylene tube. Another tube is inserted through the oesophagus towards the posterior region of the nasal cavity. The passage of the nasopalatine tract is sealed so that the drug solution is not drained from the nasal cavity through the mouth. The drug solution is delivered to the nasal cavity through the nostril or through the cannulation tubing. Femoral vein is used to collect the blood samples. As all the probable outlets of drainage are blocked, the drug can be only absorbed and transported into the systemic circulation by penetration and/or diffusion through nasal mucosa.
- **Rabbit model**
  The rabbit offers several advantages as an animal model for nasal absorption studies:
  - It permits pharmacokinetic studies like large animals (like monkey)
  - It is relatively cheap, readily available and easily maintained in laboratory settings
  - The blood volume is large enough (approx. 300ml)
  - Allows frequent blood sampling (l-2ml). Thus, it permits full characterization of the absorption and determination of the pharmacokinetic profile of a drug. Rabbits (approx. 3 kg) are either anaesthetized or maintained in the conscious state depending on the purpose of study. In the anaesthetized model, intramuscular injection of a combination of ketamine and xylazine is given to anaesthetized rabbit. The rabbit's head is held in an upright position and nasal spray of drug solution is administered into each nostril. The body temperature of the rabbit is maintained at 37°C during experiment with the help of a heating pad. The blood samples are collected by an indwelling catheter in the marginal ear vein or artery.

***Ex-vivo* Nasal Perfusion Models**

Surgical preparation is the same as that is for *in-vivo* rat model. During the perfusion studies, to minimize the loss of drug solution a funnel is placed between the nose and reservoir. The drug solution is placed in a reservoir maintained at 37°C and is circulated through

the nasal cavity of the rat with a peristaltic pump. The perfusion solution passes out from the nostrils (through the funnel) and runs again into the reservoir. The drug solution in the reservoir is continuously stirred. The amount of drug absorbed is estimated by measuring the residual drug concentration in the perfusing solution.

Rabbit can also be used as the animal model for ex- vivo nasal perfusion studies. The rabbit is anaesthetized with parenteral uretliane-acepromazine. A midline incision is made in the neck and the trachea is cannulated with a polyethylene neonatal endo- tracheal tube. The oesophagus is isolated and ligated. The distal end of the oesophagus is closed with suture and flexible tygon tubing is inserted into the proximal end and advanced to the posterior part of the nasal cavity. To avoid drainage of drug solution from the nasal cavity the nasopalatine tract (that connects nasal cavity to the mouth) is closed with an adhesive. The drug in isotonic buffer solution is recirculated using a peristaltic pump.

***In-vivo* bioavailability studies**

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

**Applications**

**Local Delivery** [199]

For the natural treatment of topical nasal disorders the drug is administered through nasal route. In fact, relatively low doses are effective when administered through nasal route with less systemic toxic effects.eg: Anti-histamines for rhino sinusitis and nasal decongestants for common cold.[200-206]

**Systemic Delivery** [199]

The intranasal administration of drugs is an effective way for systemic availability of drugs as compared to oral and intravascular routes. Actually, it seems to present fast and extended drug absorption, and it has been supported by many studies planned to compare intranasal drug delivery against oral and parenteral administration. E.g: analgesic (morphine), cardiovascular drugs (propranolol, carvedilol), hormones (levonorgestrel, progesterone, insulin), anti-inflammatory (indomethacin, ketorolac) and anti-viral (acyclovir). [207- 217]

**Vaccine Delivery**

Mucosal site gives first line of defense against the microorganisms entered into the body, nasal mucosa act by filtering the pathogens from the inspired air by compaction and MCC. Nose with NALT acts as an effective site of immune system, it is called Waldeyer´s Ring in human beings and nasal secretions mainly contains immunoglobulins (IgA, IgG, IgM, IgE), protective proteins such as complement as well as neutrophils and lymphocytes in the mucosa.[218- 220]

Nasal delivery of vaccines has been reported not only to produce systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection.[218] 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 eliminate the pathogen before it becomes established.[220]

Recently, for the diseases like anthrax and influenza are treated by using the nasal vaccines prepared by using the recombinant Bacillus anthracis protective antigen and chitosan respectively.[227, 127] The common diseases like measles, pertussis, meningitis and influenza causing pathogens are mainly enter into the body through the nasal mucosal surfaces and hence good candidates for nasal vaccines.

**Main reasons for exploiting the nasal route for vaccine delivery**

- The nasal mucosa is the first site of contact with inhaled antigens
- The nasal passages are rich in lymphoid tissue NALT. NALT is known as Waldeyer's ring in humans
- Adenoid or nasopharyngeal tonsils.
- Bilateral lymphoid bands
- Bilateral tubal and facial or palatine tonsils
- Bilateral lingual tonsils
- Creation of both mucosal (sIgA) and systemic (IgG) immune responses
- Low cost, patient friendly, non-injectable, safe.

**Delivery of Non-Peptide Pharmaceuticals**

Low molecular weight (below 1000 daltons) small non-peptide lipophilic drugs are well absorbed through the nasal mucosa even in the absence of permeation enhancers. Nasal membrane containing epithelium is highly 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%.[222, 223] These drugs can reach widespread circulation within few minutes after dosing, as the venous blood passes from the nose directly into the systemic circulation.

In fact, many drugs that are administered intranasally are often absorbed faster and more efficiently than those from oral administration of 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: 17ß-estradiol, progesterone, norethindrone and testosterone.
3) Vitamins: vitamin B
4) Cardiovascular drugs: hydralazine, Angiotensin II antagonist, nitroglycerine, isosorbide dinitrate, propranolol, and colifilium tosylate.
5) Autonomic nervous system drugs:
   a) Sympathomimetics: Ephedrine, epinephrine, phenylephrine,
   b) Xylometazoline, dopamine and dobutamine.
   c) Parasympathomimetics: nicotine, metacholine
   d) Parasympatholytics: scopolamine, atropine, ipatropium
   e) Prostaglandins
6) Central nervous systems stimulants: cocaine, lidocaine
7) Narcotics and antagonists: bupemorphine, naloxone
8) Histamine and antihistamines: disodium cromoglycate, meclizine
9) Anti-migraine drugs: diergotamine, ergotamine-tartarate
10) Penicillins, cephalosporins, gentamycin
11) Anti-virals: Phenyl-p-guanidine benzoate, enviroxime.
12) Inorganic compounds: Inorganic salts, colloidal gold, colloidal carbon, colloidal silver

**Delivery of Peptide-Based Pharmaceuticals**

Peptides & proteins have a generally low oral bioavailability because of their physico-chemical instability and susceptibility to hepato-gastrointestinal first-pass elimination. Examples are insulin, calcitonin, pituitary hormones etc.[224] These peptides and proteins are hydrophilic polar molecules of relatively high molecular weight, are poorly absorbed across biological membranes with bioavailabilities obtained in the range of 1–2% when administered as simple solutions. To overcome this problem mainly we are using the absorption enhancers like surfactants, glycosides, cyclodextrin and glycols to increase the bioavailability. Nasal route is proving to be the best route for such biotechnological products.

**Delivery of Drugs to Brain through Nasal Cavity**

This delivery system is beneficial in conditions like Parkinson's disease, Alzheimer's disease or pain because it requires rapid and/or specific targeting of drugs to the brain. The development of nasal delivery system to brain will increase 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 potential for certain compounds to circumvent the blood-brain barrier and enter into the brain. The recent studies express neurotrophic factors such as NGF, IGFI, FGF and ADNF have been intranasally delivered to the CNS shows good results to increase the bioavailability of drug in the brain. 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 cavity.[20]

**Delivery of Diagnostic Drugs**

Nasal drug delivery system also plays very important role in the delivery of diagnostic agents for the diagnosis of various diseases and disorders in the body. Because the intranasal route better for systemic release of medicament into blood circulation, so can get quick results with less toxicity. Phenol sulfonphthalein is a diagnostic agent used to diagnose the kidney function of the patients. Pancreatic disorders of the diabetic patients are diagnosed by using the 'Secretin' and the secretory function of gastric acid are determined by Pentagastrin, diagnostic agent.[20]

**Delivery of Protein /Macromolecules to CNS**

The oral administration of protein shows relatively low bioavailability due to their large molecular size and rapid enzymatic degradation.[25] Because of their physicochemical instability and susceptibility to first pass elimination, peptide/protein drugs are generally administered parenterally. Most nasal formulations of peptide/protein drugs have been made up in simple aqueous or saline solutions with preservatives. Absorption enhancers are also used to increase the bioavailability. Surfactants, glycosides, cyclodextrin and glycols are used as absorption enchancers.[225] They improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal blood flow, decreasing mucus viscosity, and enzyme inhibition.[226]

**Delivery of Small Molecules to the CNS**

Many small molecules have been shown to be transported directly to the brain and/or CSF from the nasal cavity. The powder formulation of elcatonin utilizing CaCO3 improves the nasal bioavailability by increasing residence time in the nasal cavity and thus enhances the systemic bioavailability.[227]The properties of small molecules, including size and lipophilicity increases delivery to the CNS following intranasal administration.[229-230] This suggests that after nasal administration morphine may be able to reach CNS more rapidly than after i.v. administration.[114]

**Cyclodextrins**

Cyclodextrins are a group of cyclic oligosaccharides capable of forming inclusion complexes with many drugs. Through CD complexation, the aqueous solubility of some hydrophobic drugs can be enhanced without changing their molecular structure and their intrinsic abilities to permeate biological membranes. In nasal preparations, co-administration of CDs has been reported to increase nasal absorption and the efficacy of poorly water soluble drugs. It is seen that CDs act as true carriers by keeping hydrophobic drug molecules in solution and increases nasal absorption. CDs increase aqueous stability and bioavailability of drugs. [231]

**Chimeric peptides**

Synthesized chimeric peptides are another possibility for the drug delivery to the brain. Chimeric peptides are generated by linking of a drug which lacks transport at BBB to a vector at the luminal membrane of brain capillary endothelial cells. The vector initiates receptor - mediated or adsorption - mediated transcytosis.[232]

**Work Done In Nasal Drug Delivery System and Marketed Products Table[12, 13]**

**Needs and Future Prospective of Nasal Drug Deivery [35]**

In the field of drug delivery, drug delivery technology plays a key role in the success of the industry. The need for non-invasive drug delivery systems continues due to poor acceptance and compliance with the existing delivery systems. The current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of poorly absorbed drugs.

Key issues facing the biopharma industry are to improve safety, improve efficacy for organ targeting, and improved compliance via sustained release or increasing residence time of drug at the site of application. New technologies include improved nasal formulations; site specific release, carrier based systems, advanced spray formulations; atomized mist technology, preservative free system and integrated formulation development are strictly needed for success of drug delivery through nasal mucosa.

For success of nasal drug delivery:

- ✓ Development of delivery technologies to increase efficacy and reduce side effects.
- ✓ Development of new technologies to deliver macromolecules with utilization of biotechnology and high technology
- ✓ Development of integrated/improved nasal formulations
- ✓ Development of integrated device for successful delivery of therapeutics.

**CONCLUSION**

Nasal drug delivery system is a promising alternative route of administration for the several systemically acting drugs with poor bioavailability and it has advantages in terms of improved patient acceptability and compliance compared to parenteral administration of drugs. This delivery system is beneficial in conditions like Parkinson's disease, Alzheimer's disease or pain because it requires rapid and/or specific targeting of drugs to the brain and it is a suitable route to produce immune response against various diseases like anthrax, influenza etc., by delivering the 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 also novel nasal products for treatment of long-term illnesses, such as diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis, will also be marketed. In present time the novel approach of this drug delivery system are investigated because the novel approach is target oriented and decrease the side effect of drug.

**CONFLICT OF INTEREST**

No conflict of interest.

**Table 1: Structural feature of different sections of nasal cavity and their relative impact on permeability[2]**

| Region | Structural features | Permeability |
|---|---|---|
| Nasal vestibule | Nasal hairs(vibrissae) epithelial cells are stratified, squamous and keratinized sebaceous glands present | Least permeable because of the presence of keratinized cells |
| Atrium | Transepithelial region stratified squamous cells present anteriorly and pseudo stratified cells with microvilli present posteriorly | Less permeable and it has small surface area and stratified cells are present anteriorly |
| Respiratory region (inferior turbinate, middle turbinate, superior turbinate) | • Pseudostratified ciliated columunar cells with microvilli (300 per cell), large surface area.<br>• Receives maximum nasal secretions because of the presence of seromucus glands, nasolacrimal duct and goblet cells.<br>• Richly supplied with blood for heating and humidification of inspired air, presence of paranasal sinuses. | Most permeable region because of large surface area and rich vasculature |
| Olfactory region | • Specialized ciliated olfactory nerve cells for small perception.<br>• Receives ophthalmic and maxillary divisions of trigeminal nerve.<br>• Direct access to cerebrospinal fluid | Direct access to cerebrospinal fluid |
| Nasopharnyx | Upper part contains ciliated cells and lower part contains squamous epithelium | Receives nasal cavity drainage |

**Table 2: Possible pathways of drug absorption**

| SUBSTANCE | POSSIBLE PATHWAYS |
|---|---|
| Dopamine[51] | Nasal mucus membrane – CSF and serum (detected within 15 minutes after administration) |
| Estradiol[52] | Nasal membrane – CSF (within 1 minutes) |
| Progesterone[53] | Nasal membrane – olfactory dendrites –nervous system supporting cell n olfactory mucosa – submucosal blood vascular system – CSF (within 1 minute) |
| Lead carbonate[54] | Dissolved in nasal mucus and then absorbed solution |
| Chloride salt[55] | Nasal membrane – blood circulation |
| Distilled water | Nasopharnyx – cervical lymph. |
| Albumin<br>Albumin (labelled with Evans blue and horseradish peroxidise) | Nasal mucosa – sensory nerve cells of olfactory epithelium – subarachnoid space -bloodstream |
| Egg albumin | Nasal mucosa – lymphatic stream |
| Amino acids (arginine, glutamic acid, glycine, proline, serine) | Nasal mucosa – blood vessel (active transport)<br>Nasal mucosa – olfactory nerve fiber - CNS |

**Table 3: Theories of mucoadhesion**

| Theory | Mechanism of mucoadhesion | Comments |
|---|---|---|
| Electronic theory | Attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material | Electron transfer occurs between the mucin &polymer forming a double layer of electric charge at the interface |
| Adsorption theory | Surface forces resulting in chemical bonding | *Strong primary forces*: covalent bonds<br>*Weak secondary forces*: ionic bonds, hydrogen bonds and van derWaal's forces |
| Wetting theory | Ability of bioadhesive polymers to spread and develop intimate contact with the mucus membrane | Spreading coefficients of polymers must be positive Contact angle between polymer and cells must be near to zero |
| Diffusion theory | Physical entanglement of mucin strands and the flexible polymer chains Interpenetration of mucin strands into the porous structure of the polymer substrate | For maximum diffusion and best bioadhesive strength: solubility parameters ($\delta$) of the bioadhesive polymer and the mucus glycoproteins must be similar |
| Fracture theory | Analyses the maximum tensile stress developed during detachment of the BDDS from the mucosal surfaces | Does not require physical entanglement of bioadhesive polymer chains and mucin strands, hence appropriate to study the bioadhesion of hard polymers, which lack flexible chains |

**Table 4: Drugs for transmucosal delivery**

| Compound | Class | Indication | Investigation/ product development/ product and country (example) | Reference |
|---|---|---|---|---|
| Apomorphine | Dopamine agonist | Parkinson's disease (on- off symptoms) | Product development | 93,94 |
| Buserelin | Peptide | Prostate cancer | Profact, germany | 95 |
| Butorphanol | Opioid | Migraine | Stadol, USA | 96 |
| Calcitonin | Protein | Osteoporosis | Karil, gemany | 97 |
| Cobalamin (vitamin $B_{12}$) | Vitamin | Substitution of vitamin $B_{12}$ | Nascobal, USA | 98 |
| Desmopressin | Protein | Diabetes insipidus centralis, enuresis, nocturna | Mnirin, germany | 99 |
| Diazepam | Benzodiazepine | Sedation, anxiolysis, status epileptics | Product development | 100 |
| Estradiol | Steroid | Substitution of esrtradiol | Aerodiol, UK | 101, 102 |
| Fentanyl | Opiate | Analgesia, postoperative pain and agitation in children | Instanyl, germany | 103 |
| Gonadorelin | Hormone | Undescended testicle | Kryptocur, germany | 37 |
| Human growth hormone | Peptide | Growth hormone deficiency | Investigation | 104 |
| Influenza vaccine, live attenuated | Vaccine | Flu prevention | Flu mist, USA | 105 |
| Insulin | Peptide | Diabetes mellitus | Investigation | 106 |
| Ketamine | NMDA antagonist | Analgesia | Product development: Erkesa | 107 |
| L- Dopa | Non proteinogenic antagonist | Parkinson's disease | Investigation | 108 |
| Melatonin | Hormone | Jet lag | Investigation | 109 |
| Metaclopramide | $D_2$ receptor antagonist | Anti- emesis | Pramidin, Italy | 110, 111 |
| Midazolam | Benzodiazepine | Sedation, anxiolysis, status epileptics | Investigation | 112, 113 |
| Morphine | Opiate | Analgesia | Product development: Rylomine | 114 |

**Table 5: Bioadhesive polymers used in nasal drug delivery system[49]**

| Polymer | Characteristics |
|---|---|
| Cellulose derivatves<br>Soluble: hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxy methyl cellulose<br>Insoluble: microcrystalline cellulose,ethyl cellulose | Prolong the residence time of drug in nasal cavity<br>Sustain the release of drug due to high viscosity<br>Act as absorption enhancer<br>Effectively increase nasal bioavailability |
| Polyacrylates: carbomers, polycarbophils | Excellent mucoadhesive and gel forming capability<br>Capable of attaching to mucosal surfaces hence ensure intimate contact between the formulation and membrane surface |
| Starch: maize starch, degradable starch microsphere | Effectively improve absorption of both small hydrophobic and hydrophilic macromolecular drugs<br>Mostly used in mucoadhesive microparticulate nasal drug delivery system |
| Chitosan | Insoluble at neutral and alkaline pH<br>It can form water soluble salts with organic and organic acids<br>Low cost, biodegradable and biocompatible |

**Table 6: Excipients in nasal drug delivery system[38]**

| S.no | Excipients name | Examples | Use |
|---|---|---|---|
| 1 | Bioadhesive polymer | hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxy methyl cellulose<br>chitosan | Prolong the residence time of drug in nasal cavity<br>Effectively enhanced intranasal bioavailability |
| 2 | Gelling agent | hydroxypropyl cellulose | Prolonging the therapeutic effect of nasal preparation |
| 3 | Penetration enhancer | Solvents<br>Alkyl methyl sulphoxides<br>Pyrrolidones<br>Surfactants | Increase the permeation of drug |
| 4 | Buffer | - | Alter the pH of the dose |
| 5 | Solubilizers | Glycols, Alcohol, Diethyleneglycolmonoethylether, Labrasol | Increase the solubility of the drug |
| 6 | Preservatives | Parabens, Phenyl ethyl alcohol, EDTA, Benzalkonium chloride, Benzoyl alcohol | Avoid the degradation of drug and preserve the formulation |
| **7** | Antioxidants | Sodium bisulphite<br>Butylated hdroxy toluene<br>Sodium meta bisulphite<br>Tocopherol | Prevent the oxidation of active ingredients |

**Table 7: Liposome – encapsulated drugs studied for nasal administration**

| Drug | Results | Reference |
|---|---|---|
| Diphenhydramine | Increased drug retention in the nasal | 160 |
| HIVgp160 – encapsulated haemagglutinating virus | HIV specifc humoral and cellular immunity in mucosal and systemic sites | 161 |
| Meningococcal OpaB and OpaJ proteins | Induced highly significant anti- Opa responses | 162 |
| Influenza virus haemagglutinin from 3 viral strains | Provides an almost total prevention of virus shedding combined with a high level of immunological protection against homologous virus challenge | 163 |
| Trivalent influenza A/ H1N1 – proteosome | Produced high antibody titers in serum as well as in nasal secretions | 164 |
| Salmon calcitonin | Ultra – flexible liposomes significantly enhanced the hypocalcaemia effect than conventional liposomes | 165 |
| Ovalbumin in an archacal lipid mucosal vaccine adjuvant and delivery (AMVAD) | Eliciting robust antigen – specific mucosal and systemic immune responses | 166 |
| Tetanus toxoid antigen | Effective mucosal immune responses and high mucosal secretory IgA titers | 167 |
| M. tuberculosis vaccines (DNA – hsp65) | Effective protection against TB with a single dose vaccination | 168 |

**Table 8: Various intranasal drug delivery systems and their purpose[46]**

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

**Table 9: Delivery means and devices for intranasal administration of drugs[176]**

| Drugs | Delivery devices |
|---|---|
| Adrenal corticosteroids jelly | Nasal spray, nasal drops, nasal insufflators, sub mucosal injections into anterior tip of inferior turbine, metered dose aerosol |
| Antihistamines | Nasal spray, nasal drops |
| Buserelin Formulations | Nasal spray, ointment |
| Calcitonin | Nasal drops |
| Cocaine | Nasal spray, nasal drops, cotton pledget, gauge packtail, insufflator, rubbng with cocaine mud |
| Dopamine | Nasal spray |
| Estradiol - 17$\beta$ | Nasal spray, nasal drops, micro syringe |
| Gentamicin | Nasal spray |
| Hyoscine ( scopolamine) | Nasal spray, nasal drops |

**Table 10: Liquid nasal devices[175]**

| S. No | Devices | Drug | Dosing | Use |
|---|---|---|---|---|
| 1 | Squeezable bottle | Decongestants | Multiple dose | Common cold rhinitis |
| 2 | Vapor inhaler | Menthol | Multiple dose | Common cold |
| 3 | Multi dose metered | Topical steroids | Multiple dose | Allergic & perinneal rhinitis |
| 4 | Dose spray pump | Desmopressin | Multiple dose | Primary nocturnal enuresis |
| 5 | Pulsation membrane nebulizer | Topical steroids | Multiple dose | Sinusitis and nasal polyps |
| 6 | Vibrating mechanical nebulizer | Topical drugs | Multiple dose | Sinusitis and nasal polyps |
| 7 | Hand held mechanical nebulizer | Insulin | Multi dose | Alzheimer's disease |

**Table 11: Powder nasal devices[175]**

| S. No | Devices | Drug | Dosing | Use |
|---|---|---|---|---|
| 1 | Powder spray device | Zolmtriptan | Single dose | Migraine |
| 2 | Powder spray | Active agent | Single dose | - |
| 3 | Insufflators | Active agent | Single dose | Allergic rhinitis |
| 4 | Breath powder bi directional delivery | Sumatriptan | Single dose | Migraine |
| 5 | Single/duo dose capsule inhaler | dexamethasone | Single/duo dose | Allergic rhinitis |

**Table 12: Work done in nasal drug delivery system**

| S. No | Drug | Dosage form | Method/polymer | Inference | Reference |
|---|---|---|---|---|---|
| 1 | Indomethacin | Nasal gel | Poloxamer- 407<br>Carbopol - 934 | Improved drug solubility and permeation properties | 178 |
| 2 | Ondansteron Hcl | Nasal spray | β – cyclodextrin<br>HPMC | Decrease the dose size by minimizing first pass effect | 179 |
| 3 | ciprofloxacin | Microspheres | Emulsion solvent diffusion method | Increase bioavailability of drug | 180 |
| 4 | Chlorhexidine Hcl | Nasal gel | Poloxamer – 188<br>Poloxamer – 407<br>Carbopol 934P | The drug show sustained release | 181 |
| 5 | Salbutamol | Nasal gel | HPMC | Enhanced bioavailability and decrease the dose | 182 |
| 6 | olanzapine | Microemulsions | Water titration method | Brain targeting study | 183 |
| 7 | Ondansteron Hcl | Nasal gel | Pluronic F - 127 | Reducing the dose of drug | 184 |
| 8 | Metaclopromaide Hcl | Nasal gel | Gellan gum, xanthan gum | Enhancing patient compliance | 185 |
| 9 | Metaprolol tartrate | Nasal solution | HPMC K4M<br>HPMC K15M | Increased nasal residence time so improved bioavailability | 186 |
| 10 | Atenolol | Microspheres | Spray drying method | Increase bioavailability and reduce dose size | 187 |
| 11 | Atenolol | Microspheres | HPMC K15M | Maximum utilization & efficacy of the drug | 188 |
| 12 | artemether | Nano emulsion | Tween 80 | Enhanced permeation | 189 |
| 13 | Gentamicin sulphate | Microspheres | Emulsification techniques | Improved bioavailability | 190 |
| 14 | Rizatriptan benzoate | microparticulate | Spray drying method | Improved bioavailability | 191 |
| 15 | Progesterone | Nasal gel | Carbopol | Increased in plasma level | 192 |
| 16 | Rizatriptan benzoate | Nasal gel | Thermoreversible system | Improved bioavailability | 193 |
| 17 | Rizatriptan benzoate | Nano emulsion | Pseudo ternary phase | Brain targeting | 194 |
| 18 | Domperidone | microsphere | Emulsification crosslinking techniques | Target oriented | 195 |
| 19 | Active agent | Hydrogel | Chitosan<br>PEG | Increase the absorption of drug | 196 |
| 20 | Active agent | Nanoparticulate | Chtosan<br>PEG | Improved immunogenic response | 197 |
| 21 | Diazepam | Nasal gel | HPMC<br>Carbopol 934 | Improved bioavailability | 198 |

**Table 13: Marketed products[133]**

| S. No | Product | Drug | Indication | Manufacturer |
|---|---|---|---|---|
| 1 | BeconaseÒ AQ Nasal spray | Beclomethasone Dipropionate monohydrate | Symptomatic treatment of seasonal and perennial allergic rhinitis | Allen and Hanbury's/Glaxo wellcome Inc. |
| 2 | VancenaseÒ AQ Nasal spray | Beclomethasone Dipropionate monohydrate | Symptomatic treatment of seasonal and perennial allergic rhinitis | Schering Plough corp. |
| 3 | RhinocortÒ AQ Nasal inhaler | Budenoside | Management of symptoms of seasonal and perennial allergic rhinitis and non-allergic rhintis | Astra USA, Inc. |
| 4 | Stadol NSÒ Nasal spray | Butorphanol tartrate | Management of pain including migraine headache pain | Bristol Myers squibb |
| 5 | MiacalcinÒ Nasal spray | Calcitonin – salmon | Post – menopausal osteoporosis | Sandoz pharmaceutical corp. |
| 6 | Nasal cromÒ Nasal solution | Cromolyn sodium | Symptomatic prevention and treatment of seasonal or perennial rhinitis | Fisons corp. Prescription products |
| 7 | DDAVPÒ Nasal spray | Desmopressin acetate | Prevention and control of polydispia, polyurea, and dehydration in patients with diabetes insipidus | Rhone Poulenc Rorer |
| 8 | StimateÒ Nasal spray | Desmopressin acetate | Hemophila A, von willebrand's disease (type 1) | Rhone Poulenc Rorer |
| 9 | DecadronÒ phosphate turbinaireÒ | Dexamethasone | Treatment of inflammatory nasal conditions or nasal polyps | Merck and co., Inc. |
| 10 | NasalideÒ Nasal solution | Flunisolide | Symptomatic prevention and treatment of seasonal or perennial rhinitis | Roche Laboratories |
| 11 | FlonaseÒ Nasal spray | Fluticasone propionate | Management of seasonal and perennial rhinitis | Allen and Hanbury's/Glaxo wellcome Inc. |
| 12 | SynarelÒ Nasal solution | Nafarelin acetate | Central precocious puberty, endometriosis | Roche Laboratories |
| 13 | SyntocinonÒ Nasal spray | Oxytocin | Promote milk ejection in breast feeding mothers | Sandoz pharmaceutical corp. |
| 14 | NasacortÒ Nasal inhaler | Triamcinolone aceetonide | Treatment of seasonal and perennial allergic rhinitis | Rhone Poulenc Rorer |

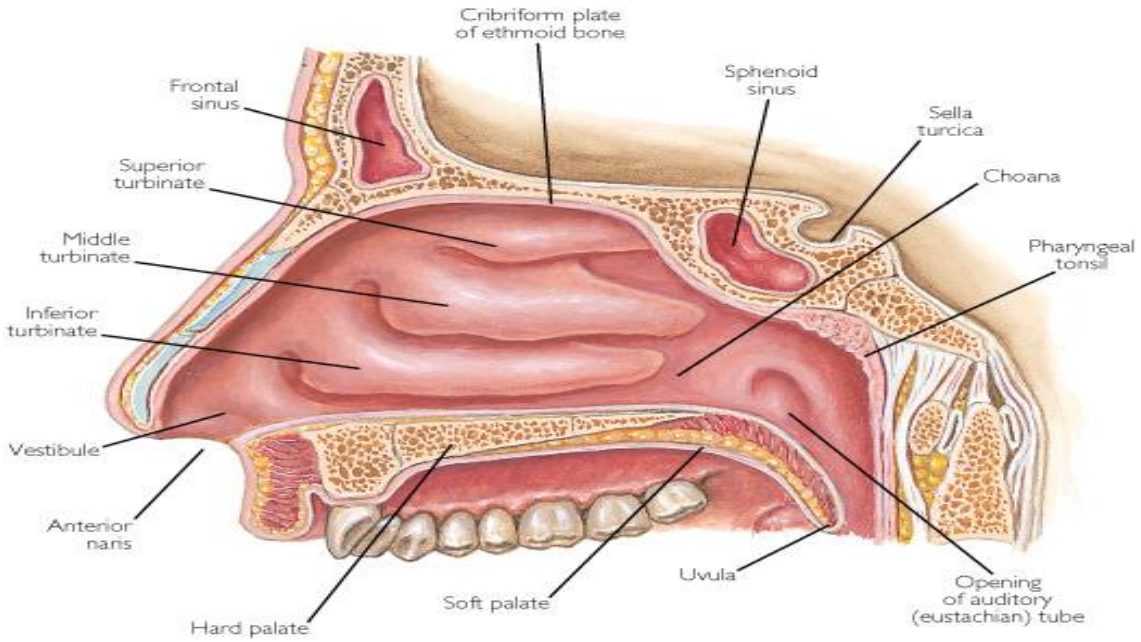


**Fig. 1: Anatomy and physiology of nasal cavity**

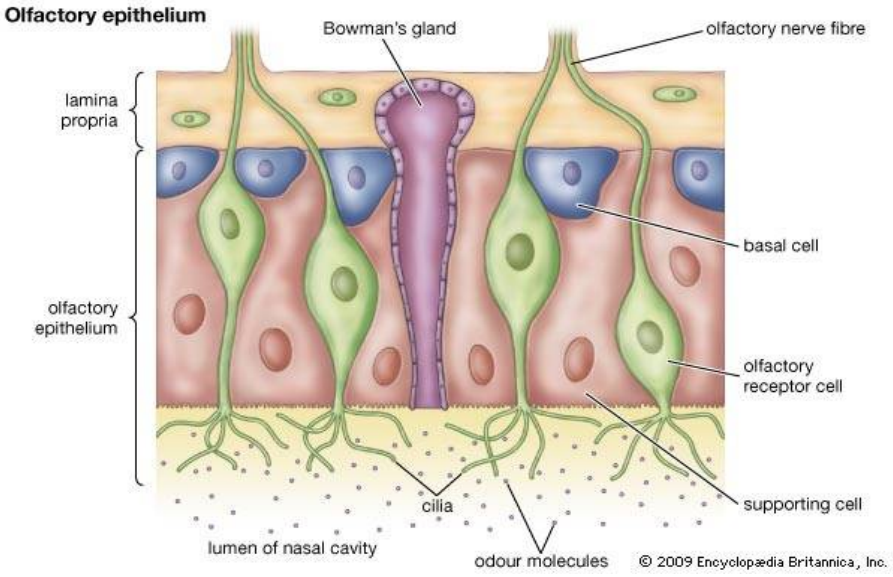


**Fig. 2: Olfactory mucosal cells types include: bipolar neurons, supporting cells, basal cells, and bowman's glands**

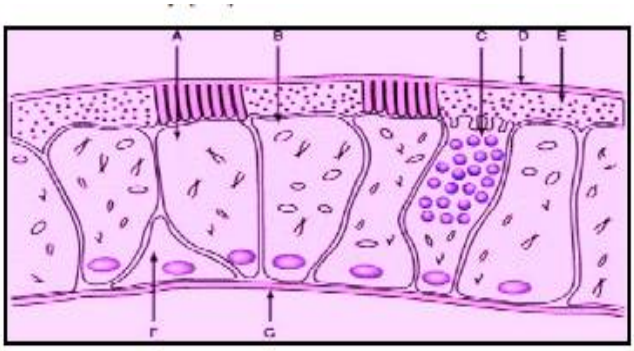


**Fig. 3: Cell types of the nasal epithelium showing ciliated cell (A), non-ciliated cell(B), goblet cells(C), gel mucus layer (D), sol layer (E), basal cell (F) and basement membrane (G)**

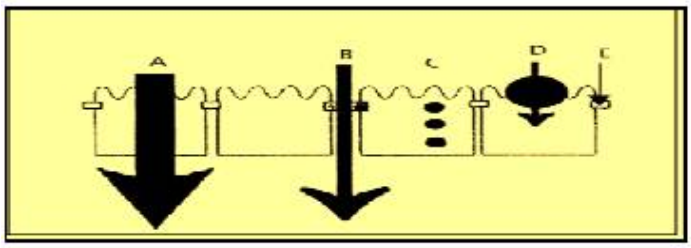


**Fig. 4: Drug transport pathways across the epithelium. (A), paracellular transport (B), transcytosis (C), Carrier mediated transport (D), and intercellular tight junction (E)**

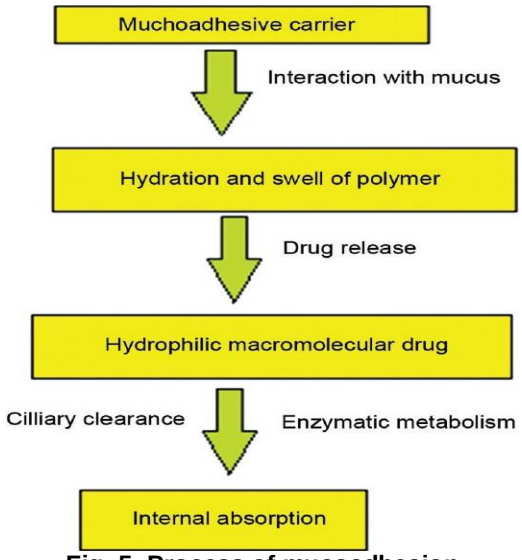


**Fig. 5: Process of mucoadhesion**

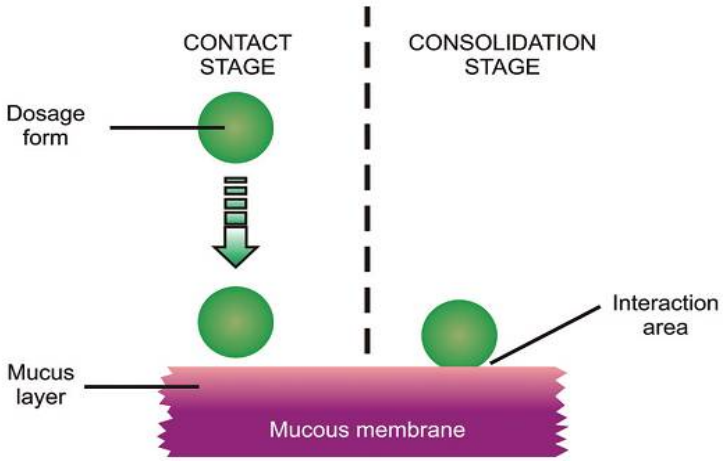


**Fig. 6: 2 steps of mucoadhesion process**

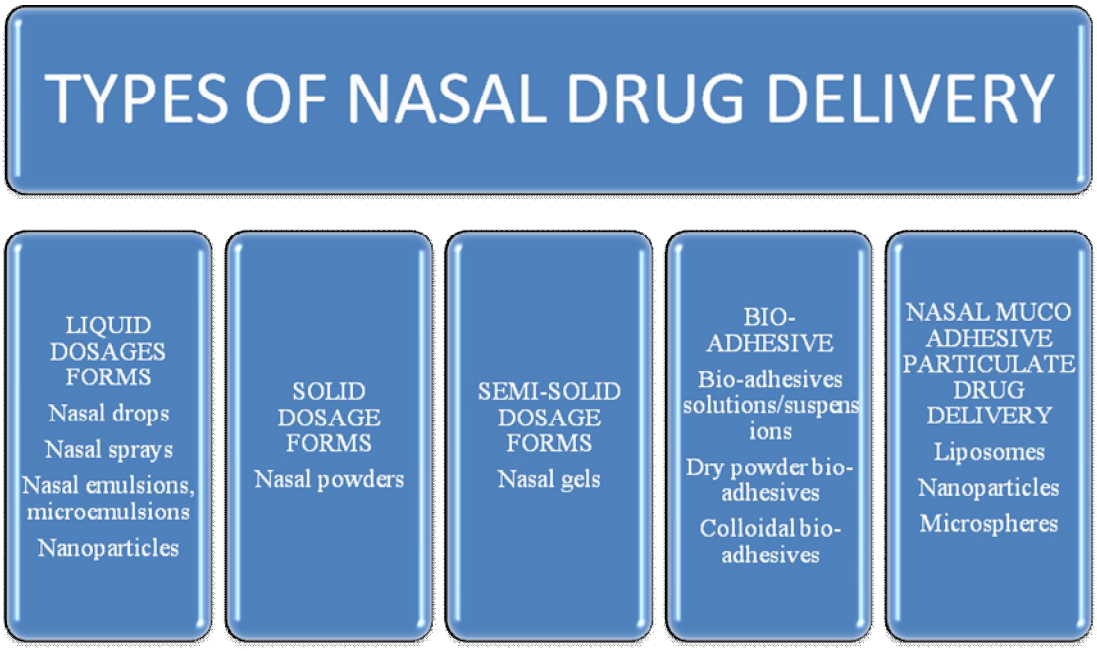


**Fig. 7: Types of nasal drug delivery**

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