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Original Research Paper NEW APPROCHES OF NASAL DRUD DELIVERY SYSTEM D.Krishnarajan\*, A.Tamilselvan, Sijo Abraham, Rohan J Mathew, S.Ramya, K.R.Raja

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# ABSTRACT

This review article focuses on providing updated information about targeting the nasal mucosa for drug delivery. The oral route is most desirable and convenient route for drug administration and tablets, capsules are the most favored dosage forms. However, although the oral route remains the most popular for systemic drug administration, low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery. The anatomy and physiology of the nasal region have been discussed, followed by a discussion of the factors and barriers affecting the drug absorption, strategies to improve the drug absorption, various excipients employed in nasal formulations, different types of nasal formulations and applications of nasal delivery. Nasal route is alternative to parenteral therapy and also useful for long term therapy. Nasal mucosa is highly vascularized and most permeable giving rapid absorption and onset of action. Nasal route is noninvasive, widely used for the local treatment may also be used for systemic therapy as drug directly goes in systemic circulation. Nasal route gives good absorption of small molecules, than that of large molecules can be increased by absorption promoters. Therefore, the aim of this review article is to discuss the various pharmaceutical dosage forms that have the potential to be utilised for local or systemic drug administration. It is intuitively expected that this review will help to understand and further to develop suitable intra-nasal formulations to achieve specific therapeutic objectives.

Keywords: Nasal Delivery, Nasal mucosa, Absorption promoters, Noninvasive, Bioavailability.

# **INTRODUCTION**

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 Avurvedic system of Indian medicines [1]. The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery routes [2]. 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 [3, 4]. The nasal delivery of drugs in the recent decade been considered as a prospective route of administration to achieve higher bioavailability and increased level of drug absorption. The nasal delivery seems to be a favorable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS) active compounds. Hence, the rationale behind this article is to provide an expan¬sive review covering the myriad aspects of nasal drug delivery.

# ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

The anatomical and physiological aspects of the nasal membrane have been studied with its relation to the drug delivery. The nasal cavity is divided into two halves by the nasal septum and extends posteriorly to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril as depicted in (Fig 1). The atrium is an intermediate region between the vestibule and the respiratory region. The respiratory region, the nasal conchae or turbinates, which occupy the major part of the nasal cavity, possess lateral walls dividing it into three sections: superior, middle and inferior nasal turbinates. These folds provide the nasal cavity with a high surface area compared to its small volume. Each cavity has a volume of approximately 7.5 mL and has a surface area around 75 cm<sup>2</sup>. The three distinct functional regions of the nose are-the vestibular, respiratory, and olfactory.<sup>[5-7]</sup>



**Figure 1:** Schematic of a sagittal section of human nasal cavity showing the nasal vestibule

(A), atrium (B), respiratory region: inferior turbinate (C1), middle turbinate (C2) and the superior turbinate (C3), the olfactory region (D) and nasopharynx

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

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

# ADVANTAGES OF NASAL DRUG DELIVERY SYSTEMS

- Easy, convenient and self administration.
- Onset of action is rapid.
- A self-administration is possible.

• Patient convenience and compliance is improved.

• Hepatic first pass metabolism is absent.

• Avoidance of irritation of the gastrointestinal membrane.

• Absorption of drug is rapid via highly vascularised mucosa.

• Availability of large nasal mucosal surface area for dose absorption.

• Bypass the BBB.

• Degradation of drug observed in GIT is avoided.

• Bioavailability of large drug molecules can be increased by means of absorption enhancers.

• Unsuitable drug candidates for oral route can be successfully given via nasal route.

• Alternate to parenteral route especially for proteins and peptides.

• Convenient route for the patient on long term therapy.

• Side effects are reduced due to low dose.

• Direct transport into systemic circulation and CNS is Possible.

• Offers lower risk of overdose.

• Does not have any complex formulation requirement.



Figure 2: Cell types of the nasal epithelium showing ciliated cell

(A), non-ciliated cell (B), goblet cells (C), gel mucus layer (D), sol layer (E), basal cell (F) and basement membrane (G)

# LIMITATIONS OF NASAL DRUG DELIVERY SYSTEMS

• High molecular weight compounds cannot be delivered through this route (mass cut off ~1 kDa).

• Normal defense mechanisms like mucociliary clearance and ciliary beating affects the permeability of drug.

- Delivery volume in nasal cavity is restricted to 25–200  $\mu L$  .

• Enzymatic barrier to permeability of drug.

• Adversely affected by pathological conditions.

• Smaller absorption surface compared with GIT.

• Possibility of nasal irritation hence inconvenient compared with oral route .

• Limited understanding of mechanisms and less developed models at this stage.

# CHARECTERISTICS OF AN 'IDEAL' DRUG CANDIDATE FOR NASAL DELIVERY

An ideal nasal drug candidate should possess the following attributes:

• Appropriate aqueous solubility to provide the

desired dose in a 25-150 ml volume of

- formulation administration per nostril.
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.

• A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.

• Low dose. Generally, below 25 mg per dose.

• No toxic nasal metabolites.

• No offensive odors/aroma associated with the drug.

Suitable stability characteristics.

# MECHANISM OF DRUG ABSORPTION FROM THE NASAL CAVITY

Initially, the absorption of drug from the nasal cavity is channeled through the mucus. Particles which are small and uncharged effortlessly pass through this layer. Large or charged particles may find it more difficult to traverse. Mucin, the chief protein of the mucus, has the potential to attach to solutes, hindering diffusion. Furthermore, environmental changes (i.e. pH, temperature, etc.) may contribute to the structural changes of the mucus layer.[10]

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



**Figure 3:** Potential drug transport mechanisms across the nasal epithelium: transcellular passive diffusion

(A), paracellular passive diffusion (B), carriermediated transport (C), absorption through transcytosis (D) and efflux transport (**E**)

# **Paracellular route:**

It includes aqueous path of transport, which is also called as the Paracellular route. This is slow and passive route. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Da,[11] because there exists an inverse relationship between molecular weight and absorption.

Transcellular route:

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

For example, Chitosan, a natural biopolymer opens tight junctions between epithelial cells to facilitate drug transport i.e. paracellular transport. [12].

# **BARRIERS TO NASAL ABSORPTION**

# Low bioavailability:

Polar drugs possess bioavailability which is generally low, i.e., not above 1% for peptides such as calcitonin and insulin and 10% for low molecular weight drugs. Low membrane permeability is the most imperative fac-tor limiting the nasal absorption of polar drugs and in particular large molecular weight polar drugs such as peptides and proteins. Drugs traverse the epithelial cell membrane either by the transcellular route, by vesicu¬lar transport receptor mediated or mechanisms, or by the paracellular route. Polar drugs with molecular weights below 1000 Da will by and large cross the membrane by means of the tran-scellular route. Larger peptides and proteins have been shown to be able to pass the nasal membrane using an endocytic transport process but only in small amounts.

# **Mucociliary clearance:**

Mucociliary clearance results in the speedy removal of the drug from the site of deposition mostly of the pep¬tide drugs. The prompt clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism is an added factor of consequence for low membrane transport. This is principally the case when the drug is not absorbed rapidly enough across the nasal mucosa. It has been shown that for both liq¬uid and powder formulations, which are not bioadhe¬sive, the halflife for clearance is of the order of 15-30 min. The use of bioadhesive excipients in the formu¬lations is an approach to overcome the rapid mucocili¬ary clearance. Mucociliary clearance can also be reduced by depositing the formulation in the anterior, less cili¬ated part of the nasal cavity thus leading to improved absorption.

# **Enzymatic Degradation:**

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

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

## **Drug Absorption Enhancement:**

Many drugs having high water solubility have poor permeability across nasal epithelia and may present insufficient bioavailability. To enhance their bioavailability permeation and permeation enhancers are frequently employed . In principle, induce enhancers permeation reversible modifications on the structure of the epithelial barrier. Although the exact mechanism of drug absorption/permeation enhancement is not well known, it is widely accepted that these materials modify the permeability of epithelial cell layer by modifying the phospholipid bilayer [13]. Different types of absorption/permeation enhancers are enlisted in Table 2 with their possible mechanism of action.

# FACTORS INFLUENCING NASAL DRUG ABSORPTION: [4,36]

Various factors affect bioavailability of nasally administered drugs as follows:-

# **I Biological Factors**

- Structural features
- Biochemical changes

# **II Physiological factors**

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

# **III Physicochemical Properties of Drugs**

- Molecular weight
- Size
- Solubility
- Lipophilicity
- pka and Partition coefficient

- Chemical form of drug.
- Polymorphism.
- Chemical state.
- Physical state.

# **IV Physicochemical Properties of Formulation**

- Physical form of formulation
- pH
- Osmolarity

• Volume of solution applied and drug concentration

• Viscosity.

# **I BIOLOGICAL FACTORS**

# 1] Structural features

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

# 2] Biochemical changes

Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and

proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result creation of a pseudo-first-pass in effect. Metabolism of nasal decongestants, alcohols, nicotine and cocaine IS due to 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.. То overcome these degradations various approaches have been used. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin.

# **II PHYSIOLOGICAL FACTORS**

# Blood supply and neuronal regulation

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

## **Nasal secretions**

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

• Viscosity of nasal secretion

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

• Solubility of drug in nasal secretions

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

• Diurnal variation

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

• pH of nasal cavity

variation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants.

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

# Mucociliary clearance (MCC) and ciliary beating

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

## **Pathological conditions:**

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

## **Environmental conditions:**

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

## Membrane permeability:

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

# III PHYSICOCHEMICAL PROPERTIES OF DRUG:

Molecular weight and size: Drug permeation is determined by molecular weight, molecular size,

hydrophilicity and lipophilicity of the compound. For compounds 1 kDa, bioavailability can be directly predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug don't significantly affect permeation of drug LT 300 Da,

which will mostly permeate through aqueous channels of the membrane. By contrast, for compounds with MW 300 Da rate of permeation is highly sensitive.

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

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

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

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

*Chemical state of drug:* Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. Chemically alter a drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides

many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated.

## 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.

# VI PHYSICOCHEMICAL PROPERTIES OF FORMULATION:

# Physical form of formulation:

Physical form of the formulation is very important in nasal drug absorption. Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery observed with more viscous formulation. Scientist found that somewhat more sustained effects of desmopressin are observed with addition of viscous agent but total bioavailability is not enhanced. Viscous formulations may help in minimizing nasal drip.

*pH:* extent of drug ionization IS determined by pH partition hypothesis hence it is related to formulation pH. Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria. Ideal formulation pH should be adjusted between 4.5 and 6.5. pH of the nasal surface is 7.39 and the pH of nasal secretions is 5.5-6.5 in adults and 5.0-6.7 in infants and children.

**Osmolarity:** Formulation tonicity substantially affect the nasal mucosa generally, an isotonic formulation is preferred. Some scientist studied the effects of formulation osmolarity, on the nasal absorption of secretin in rats. They found that all cells of the nasal mucosa were affected by the concentration sodium chloride of in the formulation and-the absorption reached а 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.

*Volume of solution applied and drug concentration:* There is no constant relationship between volume of administration and extent of absorption. Clement studied the effect of three nasal spray concentrations of cetrizine on the clinical efficacy. The results showed that 16.7%, 30.8%, 42.9%, and 26.7% of days the patients experienced appeared to improve with the drug concentration up to only 0.125%. At the higher concentration, 0.250%, the efficacy declined.

*Viscosity:* contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation.

# STRATEGIES TO IMPROVE NASAL ABSORPTION

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

1. To increase the nasal residence time.

2. To modify the drug structure to change the physicochemical properties.

3. To enhance nasal absorption.

Any one or combination of above approaches are used for the enhancing the absorption and bioavailability of the formulations.<sup>[14]</sup> Several methods have been used to facilitate the nasal absorption of drugs includes:

## **Permeation enhancers:**

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

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

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

1. Non-irritant and nontoxic.

2. Cause an effective increase in the absorption of the drug.

3. Not cause permanent damage or alteration to the tissues.

4. Effective in small amounts.

5. Compatible with other excipients.

6. Temporary and reversible.

7. Active when absorption is required.

Myriad penetration enhancers have been evaluated for organic drugs including surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetinic acid derivatives, cyclodextrins and glycols. [15].

# CLASSIFICATION OF CHEMICAL PENETRATION ENHANCER IN

o Surfactants: Polyozyethylene-9-lauryl ether (Laureth-9), Saponins

o Glycols: n-glycofurols and n-ethylene glycols

o Chelators: Salicylates, Ethylenediaminetetraacetic acid (EDTA)

oCyclodextrins:  $\alpha$ ,  $\beta$ , and  $\gamma$ - cyclodextrins and their deriv-atives

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

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

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

o Glycyrrhetinic acid derivates: Carbenozolone, Glycyr¬rhizinate

## Nasal enzyme inhibitors:

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

## **Prodrug approach:**

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

## Particulate drug delivery:

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

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

# Structural modification:

Modification of drug structure without altering pharmacological activity is one of the productive ways to improve the nasal absorption. The chemical modification of drug molecule has been commonly used to modify the physicochemical properties of a drug such as molecular size, molecular weight, pKa and solubility.

## **Excipients Used in Nasal Formulations:**

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

#### **Bioadhesive polymers:**

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

#### **Buffers:**

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

## **Penetration enhancers:**

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

#### **Solubilizers:**

Nasal drug delivery in solution form faces the

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

## **Preservatives:**

Nasal formulations are aqueous based, hence it is imperative to use preservatives. Parabens, phenyl ethyl alcohol, benzalkonium chloride, EDTA and benzoyl alcohol are some of the frequently used preservatives in nasal formulations.

#### **Antioxidants:**

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

## **Humectants:**

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

#### **Surfactants:**

Inclusion of surfactant into nasal dosage forms can amend the permeability of nasal membranes, which may assist the nasal absorption of drug. (Table 3).

# EVALUATION OF NASAL DRUG FORMULATIONS [18, 19]

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

(A) In vitro diffusion studies The nasal diffusion cell is fabricated in glass. The water-jacketed recipient chamber having total capacity of 60 ml and a flanged top of about 3mm; the lid has 3 opening, each for sampling, thermometer, and a donor tube chamber. The donor chamber is 10 cm long with internal diameter of 1.13 cm, and a donor tube chamber has total capacity of 60 ml and a flanged top of about 3mm; the lid has 3 openings, each for sampling, thermometer. The nasal mucosa of sheep was separated from sub layer bony tissues and stoned in distilled water containing few drops at genatamycin injection. After the complete removal of blood from muscosal 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 technique. The analytical temperature is maintained at 37oC throughout the experiment.

#### (B) In Vivo Nasal Absorption studies

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

**Rat model** The surgical preparation of rat for in vivo nasal absorption study is carried out as follows: The rat is anaesthetized by intraperitoneal injection of sodium pentobarbital. An incision is made in the neck and the trachea is cannulated with a polyethylene tube. Another tube is inserted through the 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:

1. It permits pharmacokinetic studies as with large animals (like monkey)

2. It is relatively cheap, readily available and easily maintained in laboratory settings

3. The blood volume is large enough (approx. 300ml)

4. To allow frequent blood sampling (l-2ml).

Thus, it permits full characterization of the absorption and determination of the pharmacokinetic profile of a drug. Rabbits (approx. 3 kg) are either anaesthetized or maintained in the conscious state depending on the purpose of study. In the anaesthetized model, intramuscular injection of a combination of ketamine and xylazine is given to anasthetized 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.

vivo Nasal Perfusion Models Surgical Ex 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 endotracheal tube. The oesophagus is isolated and ligated. The distal end of the oesophagus is closed with suture and flexible tygon tubing is inserted into the proximal end and advanced to the posterior part of the nasal cavity. To avoid drainage of drug solution from the nasal cavity the nasopalatine tract (that connects nasal cavity to the mouth) is closed with an adhesive. The drug in isotonic buffer solution is recirculated using a peristaltic pump.

# In-vivo bioavailability studies

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

# Pharmacokinetic analysis

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

# EVALUATION OF NASAL IN SITU GEL

# Clarity<sup>[20]</sup>

The clarity of in situ gel was examined by visually under dark background64.

# pH of the Gel<sup>[20]</sup>

The normal range of nasal mucosal pH is 6.2 to 7.0 pH.The advisable pH of the nasal formulation is in the range of 5.5 to 7. pH can be determined formulation is taken in beaker & 1ml NaOH added drop wise with continuous stirring. pH is checked by using pH meter48.

Drug Content<sup>[21]</sup>

Formulation was taken in a volumetric flask and then it was diluted with distilled water then volume was adjusted. Pipette out appropriate quantity from this solution, again diluted with distilled water. After this absorbance of prepared solution was measured at particular wavelength of the drug by using U.V visible spectrophotometer.65

## Viscosity Measurement<sup>[20]</sup>

The viscosity measured by using Brookfield viscometer, cone & plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity 5-1000 mPas, before gelling & after ion gel activation by eye will have viscosity of from about 50-50,000 mPas.66,67

# Measurement of Gelation temperature: (For thermosensitive approach)

The gelation temperature was described by miller & Donovan technique. In this phase transition occurred from liquid phase to a gel phase. In this 2 ml *insitu* gel transferred to test tube and placed into water bath then the temperature of water bath increased slowly and constantly. Gel was allowed to equilibrate for 5 minute at each setting, then formulation was examined for gelation. When the meniscus would no longer move upon tilting to 90°, this is known as a gelation temperature.

## Measurement of Gel strength<sup>[22]</sup>

Formulated gels were placed in the test tubes and gelled in a thermostat at 37°C. The apparatus for measuring gel strength was then placed onto the in situ gel. The time taken by the apparatus to sink to a depth of 5 cm through the prepared gel was measured for each formulation.69

Weights that detached the two vials using the following equation,

# A. Stress is calculated by the formula<sup>[23]</sup>:

Detachment Stress  $(dyne/cm^2) = M * G/A$ 

Where,

M = wt required for detachment of two vials in gm

 $\mathbf{G} = \mathbf{acceleration}$  due to gravity

A = Area of tissue exposed.

# In vitro Diffusion Study of In situ Gel<sup>[20]</sup>

In vitro release study of in situ gel solution is carried out by using Franz diffusion cell. The formulation is placed in donor compartment & freshly prepared simulated tear fluid in receptor compartment. Between receptor & donor compartment dialysis membrane is placed (0.22 µm pore size). The whole assembly is placed on thermostatically controlled magnetic stirrer. The temperature of the medium is maintained at  $37^{\circ}C\pm$  $0.5^{\circ}$ C. 1ml sample is withdrawn at predetermined time interval of 1hr for 6hrs the sample volume of fresh medium is replaced. The withdrawn sample is diluted to 10ml in volumetric flask with respective solvent & analyzed bv UV spectrophotometer at respective nm using reagent blank. The drug content calculated using an equation generated from standard calibration curve. The percentage

cumulative drug release (% CDR) calculated. The obtained data is further subjected to curve fitting for drug release data. The best fit model is checked for Krosmeyers peppas & Fickinian diffusion mechanism of their kinetics.

# In vitro Permeation Study Of Insitu Gel<sup>[24]</sup>

The *in-vitro* permeation studies are performed by the diffusion studies in a diffusion cell made of glass which consists of a donor and receiver compartment. The nasal mucosa of the sheep is used in the diffusion studies.70

# **B.** Permeability coefficient calculated from the slope of the graph:

P = Slape \* Vd/S

Where,

Vd = volume of the donor solution

S = surface area of tissue

P = permeability coefficient.

## Thermal Analysis<sup>[20]</sup>

Thermo gravimetric analysis can be conducted for in situ forming polymeric system to quantitative the percentage of water in hydrogel. Different scanning calorimetry is used to observed, if there are many changes in thermograms as compared with pure ingredients used thus indicating the interaction.

# Nasal Drug Delivery Systems:

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

# Liquid nasal formulations:

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

# **Compressed air nebulizers:**

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

# Nasal Gels<sup>[24]</sup>

Nasal gels are high viscosity thickened solutions or suspension. The deposition of the gel in the nasal cavity depends on the mode of administration. Recently, the first nasal gel containing Vitamin B12 for systemic medication has entered the market.74

# Nasal Drops<sup>[24]</sup>

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. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.75

# Nasal Sprays<sup>[24]</sup>

Nasal sprays can be formulated from solution and suspension formulations. A nasal spray can deliver an exact dose anywhere from 25 to 200  $\mu$ L. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation.76

# Nasal Powder<sup>[24]</sup>

When solution and suspension dosage forms cannot be developed, then powder form is developed. The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation.77

# Liposomes<sup>[25]</sup>

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included.78 Liposomal nasal formulation contain drug alone or with the combination of other excipients. Liposomal formulations are administered to the respiratory tract as an aerosol. The particles of the formulation have diameters of less than 50 microns.

# Instillation and rhinyle catheter:

Catheters are employed to direct the drops to a particular region of nasal cavity. The formulation is placed in the tube and one end of the tube is positioned in the nose, and the solution is delivered into the nasal cavity by blowing through the other end by mouth70,71 Dosing of catheters is determined by the filling prior to administration and this is primarily used for experimental studies only.

#### **Squeezed bottle:**

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

#### Metered-dose pump sprays:

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

## **Insufflators:**

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

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales.73 These are regularly used to treat respiratory diseases such as asthma, bronchitis, emphysema and Chronic Obstructive Pulmonary Disease (COPD) and have also been used in the treatment of diabetes mellitus. The medication is commonly housed either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into the mouth and takes a deep inhalation, holding the breath for 5-10 s. An array of such devices is available in the market. The dose that can be delivered is characteristically less than a few tenths of milligrams in a single breath since larger powder doses may lead to provocation of cough.

# **Pressurized Metered Dose Inhalers (MDIs):**

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

To use the inhaler the patient depresses the top of the canister, with the thumb supporting the lower portion of the actuator. The propellant offers the force to create the aerosol cloud and is also the medium in which the active component must be suspended or dissolved. Propellants in MDIs typically make up more than 99% of the delivered dose. Actuation of the device discharges a single metered dose of the formulation which contains the

medication either dissolved or suspended in the propellant. Disintegration of the volatile propellant into droplets, ensued by rapid evaporation of these droplets consequentially generates an aerosol consisting of micrometer-sized medication particles that are then inhaled.

#### Novel drug formulations:

Many factors, such as, stability, membrane penetration and retention time have led to the development of nasal formulations containing liposomes, microspheres and nanoparticles for intranasal drug delivery. These systems can include, besides the drug, enzymatic inhibitors, nasal absorption enhancers or/and mucoadhesive polymers.

#### **Microspheres:**

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

## Nanoparticles:

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

# APPLICATIONS OF NASAL DRUG DELIVERY SYSTEM [15]

#### **Delivery of non-peptide pharmaceuticals:**

Low molecular weight (below 1000 Da) small nonpeptide lipophilic drugs are adequately absorbed through the nasal mucosa even in the absence of a permeation enhancer. Nasal membrane containing epithelium is richly vascularized and it contains large surface area it is readily accessible for drug absorption because of the presence of nasal turbinates.

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

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

1) Adrenal corticosteroids

2) Sex hormones: 17ß-estradiol, progesterone, norethindrone, and testosterone.

3) Vitamins: vitamin B12

4) Cardiovascular drugs: hydralazine, Angiotensin II antagonist, nitroglycerine, isosorbidedinitrate, propanolol, and cloifilium tosylate.

5) Autonomic nervous system:

a. Sympathomimetics: Ephedrine, epinephrine, phenylephrine,

b. Xylometazoline, dopamine and dobutamine.

c. Parasympathomimetics: nicotine, metacholine

d. Parasympatholytics: scopolamine, atropine, ipratropium

e. Prostaglandins

6) Central nervous systems stimulants: cocaine, lidocaine

7) Narcotics and antagonists: buprenorphine, naloxone

8) Histamine and antihistamines: disodium cromoglycate, meclizine

9) Anti-migraine drugs: diergotamine, ergotamine tartrate

10) Penicillin, cephalosporins, gentamycin.

11) Antivirals: Phenyl-p-guanidine benzoate, enviroxime.

12) Inorganic compounds: Inorganic salts, colloidal gold, colloidal carbon, colloidal silver.

## **Delivery of Peptide-Based Pharmaceuticals:**

Peptides and proteins have in general, low oral bioavailability because of their physicochemical instability and vulnerability to hepato-gastrointestinal first-pass elimination. Examples are insulin. calcitonin, pituitary hormones etc. These peptides and proteins are hydrophilic polar molecules of comparatively higher molecular weight, are poorly absorbed across biological membranes with bioavailability values obtained in the region of 1-2%when administered as simple solutions. To surmount this problem, absorption enhancers like surfactants, glycosides, cyclodextrins and glycols have been used to augment the bioavailability. Nasal route is proving to be the prominent route for such biotechnological products.

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

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

# **Delivery of Vaccines through Nasal Route:**

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

1) The nasal mucosa is the first site of contacts with inhaled pathogens

2) The nasal passages are rich in lymphoid tissue

3) Creation of both mucosal and systemic immune responses

4) Low cost, patient friendly, non-injectable and safe

Nasal delivery of vaccines has been reported to not only produce systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection. Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of defense, which helps to get rid of the pathogen before it becomes established.

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

# **Delivery of diagnostic drugs:**

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

CONCLUSION

patients were diagnosed by using the 'Secretin'. And the secretory function of gastric acid was determined by Pentagastrin, diagnostic agent and indicates the nasal drug products available in the market [17].

# FDA GUIDANCE SPECIFIC TO NASAL DRUG DELIVERY

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

## FDA guidelines specific to NDAs:

In case of NDAs, the FDA recommends that in vitro BA studies be presented in NDAs for solution and suspension products, with additional in vivo BA studies for suspension products. The data would serve as a standard to characterize the *in vitro* performance, and for suspensions, the in vivo performance of the product. In case the formulation and/or method of manufacture of the pivotal clinical trial product changes in terms of physicochemical characteristics of the drug substance, the excipients, or the device characteristics, BE data using in vitro tests (for solution and suspension products) and certain conditions to guarantee that the to-be-marketed<sup>1</sup>. product (T) is comparable to very similar clinical trial batches and/or to batches utilized for stability testing (R).

# FDA guidelines specific to ANDAs:

Product equivalency is the key in case of ANDAs, hence, as per FDA instructions more than  $\pm$  5 percent<sup>3</sup>. Ugwoke variation between the test and reference product formulations is not permitted. Also it is prescribed that the inactive ingredients in the test product formulation be Qualitatively (Q1) the same and Quantitatively (Q2) essentially the same as the inactive ingredients in the formulation of the reference listed drug. The container and closure recommendations of FDA should also be complied. [29] . Ugwoke The bi mucoadhe 3-22. Arora P., issues in 967–975. Pomponi (1000)Per

Intranasal delivery of drugs is a promising alternative to other routes of administration, the main reason being its swift and non-invasive nature. It also leads to increased bioavailability of poorly bioavailable drugs. In contrast to parenteral administration of drugs, it has superior compliance and an improved patient acceptability. There is possibility in the near future that more drugs will come in the market in the form of nasal formulation intended for systemic treatment.

There is a lot of ground for optimism with respect to benefits derivable from more fundamental research and applications leading to a deeper understanding of the subject and eventually more marketed products. For the treatment of long illnesses such as diabetis, osteoporosis, fertility treatment novel nasal products are also expected to be marketed. So for the avoidance of side effect and improve effectiveness of nasal products we should pay attention to basic research in nasal drug delivery.

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![](_page_18_Picture_11.jpeg)

Table 1: Structural features and relevance of different nasal anatomical regions[8]

Destau	De mar e el 1114-2	
Region	Structural features	Permeability
Nasal vestibule	Nasal hairs (vibrissae) Epithelial cells are stratified, squamous and keratinized	Least permeable because of the presence of keratinized cells
Atrium	Transepithelial region. Stratified squamous cells present anteriorly; pseudo stratified cells with microvilli present posteriorly	Less permeable (small surface area and stratified cells are present anteriorly)
Respiratory region (inferior turbinate middle turbinate superior turbinate)	Narrowest region of nasal cavity. Pseudo stratified ciliated columnar cells with microvilli (300/cell), large surface area. Receives maximum nasal secretions due to presence of seromucus glands, nasolacrimal duct and goblet cells	Most permeable region (large surface area & rich vasculature)
Olfactory region	Richly supplied with blood for heating and humidification of inspired air, presence of paranasal sinuses. Specialized ciliated olfactory nerve cell for smell perception. Receives ophthalmic and maxillary divisions of trigeminal nerve	Direct access to cerebrospinal fluid
Nasopharynx	Direct access to cerebrospinal fluid. Upper part - ciliated cells; lower part -squamous epithelium	Receives nasal cavity drainage

Table 2. Nasal drug absorption enhancers and mechanisms

Class of compound	Example	Possible action
Fatty acids	Dideconoylphosphatidylcholine, lysophosphatidylcholine	Membrane disruption
Surfactants	Sodium lauryl sulphate, saponin, polyoxyethylene-9-lauryl ether	Membrane disruption
Bile salts	Sodium deoxycholate, sodium glycocholate, sodium taurodihydrofusidate	Open tight junctions, enzyme inhibition, mucolytic activity
Cyclodextrines and derivatives	α-, β-, γ-cyclodextrin DMβ-, HPβ-cyclodextrin	Open tight junctions, membrane disruption
Enzyme inhibitors	Bestatin, amastatia	Enzyme inhibition

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Bio-adhesive materials	Carbopol, starch microspheres, chitosan	Reduce nasal clearance, open tight junctions		

Polymer	Characteristics	
Cellulose derivatives Soluble: hydroxypropyl methylcellulose, hydroxypropyl cellulose(HPC),methyl cellulose(MC), carboxymethyl cellulose(CMC) Insoluble: ethylcellulose, microcrystalline cellulose(MCC) Polyacrylates	<ul> <li>Prolong the residence time of drug in nasal cavity</li> <li>Sustain the release of drug due to high viscosity</li> <li>Act as absorption enhancer</li> <li>Effectively increase intranasal bioavailability</li> </ul>	
-Carbomers -Polycarbophils	-Excellent mucoadhesive and gel forming capability	
Starch -Maize starch	<ul> <li>-Capable of attaching to mucosal surfaces hence ensure intimate contact between the formulation and membrane surface</li> <li>-Effectively improve absorption of both small hydrophobic and hydrophilic macromolecular</li> </ul>	
-Degradable starch microspheres (DSM) Chitosan	drugs -Mostly used in mucoadhesive micro particulate nasal delivery system	
	<ul> <li>It can form water soluble salts with inorganic and organic acids</li> <li>Low cost, Biodegradable and Biocompatible</li> </ul>	

# Table 3: Bioadhesive polymers used in nasal drug delivery

Table 4 : Marketed Nasal Drug Produ	acts[21,51,52,54,58,62,72,80,81]
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Brand Name	Drug	Dose per nasal spray	Indication	Manufacturer
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Miacalcin Nasal Spray	Calcitonin – Salmon	200 I.E.	Post – menopausal Osteoporosis	Novartis pharma
DDAVP Nasal Spray	Desmopressin acetate	0.1ml(10mcg)	Antidiuretic hormone	Ferring Arzneimitted
Stimate Nasal Spray	Desmopressin acetate	1.5mg/ml	Hemophilia A, von Willebrand's disease (type 1)	
Profact Nasal Spray	Buserelin	150mcg	Buserelin	Aventis Pharma
Synarela Nasal Spray	Nafarelin	200mcg	Endometriosis	Pharmacia
Syntocinon Nasal Spray	Oxytocin	30ml	Lactation induction	Novartis
Antepan Nasal Spray, Relefact*TRH Nasal Spray	Protirelin	1mg	Thyroid diagnostics	Aventis Pharma
Beconase AQ Nasal Spray	Beclomethasone dipropriate monohydrate	50 mcg	Seasonal and perennial allergic rhinitis	Allen and Hanbury's/Glaxo Wellcome Inc
Vancenase AQ Nasal Spray	Beclomethasone dipropriate monohydrate	84 mcg	Seasonal and perennial allergic rhinitis	Schering Plough Corp
Rhinocort Nasal Spray	Budesonide	32 mcg	Seasonal and perennial allergic rhinitis and nonallergic perennial rhinitis	Astra USA Inc
Stadol NSO Nasal Spray	Butorphanol tartarate		Migraine headache pain	Bristol Myers Squibb
Nasalcrom Nasal Solution	Cromolyn sodium		Seasonal or perennial rhinitis	Fison's Corp
Decadron phosphate	Dexamethasone		Inflammatory	Merck and

Turbinaire			nasal	Co.Inc
			conditions or nasal polyps	
Nasalide Nasal Solution	Flunisonide		Seasonal or perennial rhinitis	Roche laboratories
Flunase Nasal Spray	Fluticasone proprionate	50 mcg	Seasonal or perennial rhinitis	Allen and Hanbury's/Glaxo Wellcome Inc
Nasacort Nasa Inhaler	Triamcinolone acetonide	220 mcg	Seasonal or perennial allergic Rhinitis	Rhone Poulenc Rorer
Asco*Top Nasal Spray	Zolmitriptan	5 mg	Migraine	Astra Zeneca
Imigran* Nasal Spray	Sumatriptan	20 mg	Migraine	Glaxo SmithKline
Migranal* Nasal Spray	Dihyfroergotamine	2 mg	Migraine	Novartis Pharma
Aerodiol* Nasal Spray	Estradiol	300 mcg	Hormone replacement	Servier