An ornamental mucoadhesive particulate drug delivery system for nasal route: A Review

Mradul R Gupta1*, Brahma P Gupta2, Amit K Nagariya3, Priyanka Patel4, Rahul Pachouriya1, M S Sudeesh1
1Department of pharmaceutics, VNS institute of pharmacy, Vidyavihar, Neelbud, Bhopal (M.P.) India
2Sagar Institute of Research and Technology-Pharmacy, SIRT- Campus, Ayodhya by-pass road, Bhopal, Madhya Pradesh, India.
3School of pharmaceutical sciences, Sobhit University, Meerut (U.P.) India
4Technocrats Institute of Technology-Pharmacy, Bhopal, Madhya Pradesh, India.

ABSTRACT

Nasal drug delivery system offers lucrative way of drug delivery of both topical and systemic therapies. The high permeability, high vasculature and low enzymatic environment of nasal cavity are well suitable for systemic delivery of drug molecules via nose. The noninvasiveness and self-administrative nature of nasal delivery also attracts the formulation scientists to deliver protein and peptide compounds. When administering drugs to mucosal tissues, such as in the nasal cavity, it is helpful if the formulation stays in the right place long enough for the drug to be absorbed across the mucosa. It may, therefore, be beneficial to use a mucoadhesive agent in the formulation to achieve sufficient residence time and ultimately bioavailability will increase. This review will focus on the various bioavailability barriers in nasal drug delivery and the type of polymer which can improve the bioavailability of nasal dosage forms.

Key words: Mucoadhesion, Nasal delivery, Nasal formulations, Bioavailability.

INTRODUCTION

In recent years the nasal route has gained importance as a non-invasive drug application route that offers many advantages for the introduction of drugs into systemic circulation. Its major advantage is the rapid absorption of drugs and therefore quick onset of their effect. In addition, it has the advantage of avoiding the hepatic first-pass effect. It is not however without disadvantages, the best known of which, particularly for macromolecular drugs, are its enzymatic barriers and the low permeability of the nasal epithelium.

Nasal drug delivery may be used for either local or systemic effects. Low molecular weight drugs with are rapidly absorbed through nasal mucosa. The main reasons for this are the high permeability, fairly wide absorption area, porous and thin endothelial basement membrane of the nasal epithelium. Despite the many advantages of the nasal route, limitations such as the high molecular weight (HMW) of drugs may impede drug absorption through the nasal mucosa. Recent studies have focused particularly on the nasal application of HMW therapeutic agents such as peptide-protein drugs and vaccines intended for systemic effects. Due to their hydrophilic structure, the nasal bioavailability of peptide and protein drugs is normally less than 1%. Besides their weak mucosal membrane permeability and enzymatic degradation in nasal mucosa, these drugs are rapidly cleared from the nasal cavity after administration because of mucociliary clearance.

ADVANTAGES TO NASAL DRUG DELIVERY

The advantages of intranasal delivery.

1. Non-invasive, rapid and comfortable.
2. Bypasses the BBB and targets the CNS, reducing systemic exposure and thus systemic side effects.
3. Does not require any modification of the therapeutic agent being delivered.
4. Works for a wide range of drugs. It facilitates the treatment of many neurologic and psychiatric disorders.
6. Problem of degradation of peptide drugs is minimized up to a certain extent easy accessibility to blood capillaries.
7. Avoids destruction in the gastrointestinal tract, hepatic “first pass” elimination and gut wall metabolism, allowing increased, reliable bioavailability.
8. Direct delivery of vaccine to lymphatic tissue and induction of a secretory immune response at distant mucosal site.

PHYSIOLOGICAL ASPECTS OF NOSE

The basic functions of the nose are heating and humidification of inspired air before it reaches the lungs, olfaction, resonance, filtration of particles, mucociliary clearance, and antimicrobial, antiviral and immunological activities [1], the nasal cavity contains turbinates comprising a surface area of 150-180 cm² but allowing only a narrow pathway for the inspired air. Inhaled particles larger than 10 im are thus efficiently kept in the nose [2] at the same time as the air is heated and moistened.

Three types of mucosa cover the surface of the nasal cavity. The stratified squamous epithelium is found in close proximity to the nostrils and gradually transforms into a pseudostratified columnar epithelium, which covers most of the nasal cavity. The olfactory epithelium is situated in the upper posterior part of the nasal cavity and covers approximately 10 cm² of the human nasal cavity; in comparison, the olfactory mucosa in rodents constitutes about 50% of the nasal cavity [3].

The pseudostratified columnar epithelium of the respiratory nasal mucosa consists of a single layer of four main cell types: ciliated and nonciliated columnar cells, basal cells and goblet cells. The cells are covered by microvilli. Many, especially those in the posterior half of the nasal cavity, introduction to nasal powder sprays also have approximately 200 5 im long cilia, whose synchronized movements enable mucociliary clearance of unwanted particles from the nose.

The epithelial cells are covered by a layer of mucus, which is thought to consist of two distinct layers, each approximately 5 im in depth [4]. The cilia move in the low viscosity layer and as they project into the upper gel layer they push the mucus back to the nasopharynx at a speed of 3-25 mm/min.

The mucus, produced by the submucosal glands and goblet cells, is composed of >90% water, 0.5-5% mucins (mucous glycoproteins), 1-2% salts and 0.5-1% free proteins [5]. The mucus is slightly acidic (pH 5.5-6.5), which is thought to be important for its antibacterial properties [5]. The epithelial cells are secured in the
basement membrane, a layer of collagen fibrils.

The submucosa, which is highly vascularised and thus plays an important role in the systemic absorption of drugs, is situated under the basement membrane. The passive absorption of large, hydrophilic molecules is likely achieved paracellular, as opposed to more lipophilic molecules which may diffuse through the cells. Paracellular absorption is limited by the tight junctions connecting the epithelial cells on the apical side. The nasal mucosa is relatively permeable to drug molecules; the extent of absorption is lower than that from the lung but in the same order as that from the small intestine [7].

**ABSORPTION THROUGH NASAL MUCOSA**

The first step in the absorption of drugs from the nasal cavity is passage through the mucus. Small, unchanged particles easily pass through this layer. However, larger or charged particles may find it more difficult to cross. Mucin, the principal protein in the mucus, has the potential to bind solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e., pH and temperature) [8]. After a drug’s passage through the mucus, there are several mechanisms for absorption through the mucosa [9]. These include transcellular or simple diffusion across the membrane, paracellular transport via movement between cells, and transcytosis by vesicle carriers [10]. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and limited residence time in the cavity.

Nasal absorption is affected by molecular weight, size, formulation pH, pKa of molecule, and delivery volume among other formulation characteristics. Molecular weight still presents the best correlation to absorption [11, 12]. The apparent cut-off point for molecular weight is approximately 1,000 Daltons, with molecules less than 1,000 having better absorption [12]. Shape is also important. Linear molecules have lesser absorption than cyclic-shaped molecules [9]. Additionally, particles should be larger than 10 mm and otherwise the drug may be deposited in the lungs [11]. Hydrophilicity has been found to decrease a drug’s bioavailability. [13] pH is also an important formulation factor for drug absorption. Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption. Nasal irritation is minimized when products are delivered with a pH range of 4.5 to 6.5. Volume and concentration are also important considerations. 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 150 mL/ nostril have been suggested [9].

**BARRIERS FOR NASAL DRUG DELIVERY**

(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 [13]. The most important factor limiting the nasal absorption of polar drugs is especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability. 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 [9]. Larger peptides and proteins are able to pass the nasal membrane using an endocytotic transport process but only in low amounts.

Nasal absorption of such polar drugs can be greatly improved by coadministration of absorption enhancing agents [9]. Agents generally used for transnasal absorption includes surfactants (laureth-9, sodium lauryl sulfate), bile salts and bile salt derivatives (sodium glycocholate, sodium deoxycholate, sodium taurohydrofusidate), fatty acids and fatty acid derivatives (linoelic acid), phospholipids (lysocephatidylcholine, DDPC), various cyclodextrins (dimethyl-β-cyclodextrin, parenieral α-, β-, and γ-cyclodextrin), and cationic compounds (chitosaminarginine, poly-L-lysine). These enhancers work by a variety of mechanisms but generally they act by altering the permeability of the epithelial cell layer by modifying the phospholipid bilayers, leaching of proteins from the membrane or even stripping off the outer layer of the mucosa. Some of these enhancers also have an effect on the tight junctions and/or work as enzymatic degradation inhibitors. With such absorption enhancing agents, increased bioavailabilities were obtained, even for larger peptides such as insulin.

In animal studies it has been shown for a range of enhancing agents that there is a direct correlation between the absorption enhancing effect and the damage to the nasal mucosa [20], this is particularly true for bile salts and surfactants. For other enhancers, such as cyclodextrins and chitosan, the enhancing effect outweighs the damage caused to the mucosa. Hence, it is of great importance to consider the choice of absorption enhancer for a nasally delivered drug that is not easily absorbed, especially in terms of potential nasal and systemic toxicity.

(ii) **Mucociliary Clearance** - The general fast clearance of the administered formulation from the nasal cavity due to the 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 nonbioadhesive, the half life for clearance is of the order of 15 - 30 min [21].

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.

(iii) **Enzymatic Degradation** - Another contributing, but often less considered factor to the low bioavailability of peptides and proteins across the nasal mucosa is the possibility of an enzymatic degradation of the molecule in the lumen of the nasal cavity or during passage through the epithelial barrier. These sites both contain exopeptidases such as mono and diaminopeptidases that can cleave peptides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal peptide bonds [22]. The use of enzyme inhibitors and/or saturation of enzymes may be approaches to overcome this barrier [23]. In summary, the nose offers unique advantages as administration site for drug delivery. However, low permeability for polar and high molecular weight drugs, rapid clearance of the delivery system from the cavity and possible enzymatic degradation of the drug in the nose may be encountered. These challenges can be faced by various approaches, such as use of bioadhesive systems and absorption enhancers.

**MECHANISM OF DRUG ABSORPTION**

The first step in the absorption of drug from the nasal cavity is passage through the mucus. Small, unchanged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross. Mucin, the principle protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e., pH, temperature, etc.). Subsequent to a drug’s passage through the mucus, there are several mechanisms for absorption through the mucosa. These include transcellular or simple diffusion across the membrane, paracellular transport via movement between cell and transcytosis by vesicle carriers [24]. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and limited residence time in the cavity. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.

- The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons [25].

- The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For example, Chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport [26].

**MUCOADHESION**

When administering drugs to mucosal tissues, such as in the nasal cavity, it is helpful if the formulation stays in the right place long enough for the drug to be absorbed across the mucosa. It may, therefore, be beneficial to use a mucoadhesive
agent in the formulation to achieve sufficient residence time. Mucoadhesion, as
the word suggests, refers to adhesion of matter to a mucus layer for an extended
period of time [27].

A mucoadhesive agent is thus a substance that adheres to mucus. The
term bioadhesion is less specific and can be used to denote adhesion to any
biological surface. Mucoadhesive agents are usually polymers containing hydrogen
bonding groups that can be used in wet formulations, in dry powders.

The mechanisms behind mucoadhesion have not yet been fully elucidated, but a
theory that has stuck is that close contact must first be established between the
mucoadhesive agent and the mucus, followed by interpenetration of the
mucoadhesive polymer and the mucin and finishing with the formation of en-
tanglements and chemical bonds between the macromolecules.

In the case of a dry polymer powder, the initial adhesion is most likely
achieved by water movement from the mucus onto the formulation, which has
also been shown to lead to dehydration and strengthening of the mucus layer[28].

The subsequent formation of van der Waals, hydrogen and, in the case of a
positively charged polymer, electrostatic bonds between the mucins and the hy-
drated polymer promotes prolonged adhesion. A predicament with trying to in-
crease the contact time by adhesion to mucus is that the residence time of the
mucus itself is limited by mucociliary clearance. The normal transit time of a
particle deposited on top of the nasal mucus layer is approximately 12-15 min.

However, dehydration of the mucus layer on contact with the mucoadhesive
powder will increase the mucus viscosity and subsequently decelerate its clearance
[29]. Dry powder formulations should hence be especially well suited for nasal ad-
ministration as increased mucous viscosity would lower the normal requirements for
the formation of secondary chemical bonds in order to prolong residence time.

FACTOR AFFECTING MUCOADHESION

There are several factors which affect the process of mucoadhesion and
bioavailability which posses a challenge for the formulation scientist. Some of the
factor which affects the process of mucoadhesion are as under.

A. Polymer related factors:

1. Molecular weight of drug

Absorption through nasal mcosa is apparently inversely related to molecular
weight of drug molecules. In the absence of permeation enhancer, nasal absorption
is sharply reduced for drug with molecular weight over 1000 Da[30].

2. pH of polymer

The pH of a nasal formulation is important for the following reasons:
- To avoid irritation of nasal mcosa;
- 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; and
- To sustain normal physiological ciliary movement.

3. Swelling

It is important that the swelling hydration rate should not be too rapid in order to
prolong the adhesion time. However, inordinate swelling is eventually required to
reduce polymer adhesiveness and to allow it to detach from the biological tissue.

4. Chain flexibility

Chain flexibility is critical for interpenetration and entanglement of mucoadhesive
polymers. As water soluble polymers become cross-linked, mobility of individual
polymer chains decrease and thus the effective length of the chain that can
penetrate into the mucous layer decreases, which reduces bioadhesive strength.

The increased chain interpenetration can be achieved by increasing the structural
flexibility of the polymer this can be done by incorporation of poly (ethylene glycol) [31].

5. Charge on the polymer

B. Environment related factors:

1. Initial contact time

It has been reported that increased contact time and applied pressure increase
the adhesiveness of a polymer. The polymer type also plays a part. For example,

polymethacrylamide required a critical applied pressure for adhe-
sion to occur, where polyaacrylic acid and polyacrylamide acid requires no applied
pressure for interaction with mucus.

2. Effect of enzymatic activity

Several enzymes that are present in the nasal mucosa might affect the stability of
drugs. For example, proteins and peptides are subjected to degradation by pro-
teases and amino-peptidase at the mucosal membrane. However the level of
amino-peptidase present is much lower than that in the gastrointestinal tract.
Pepitides may also form complexes with immunoglobulin (IgA) in the nasal cavity
leading to an increase in the molecular weight and a reduction in permeability.

C. Physiological Factors:

Factors related to the nasal physiology include: mucociliary clearance; pathologi-
cal conditions such as infections, allergy, nasal obstruction, Kartagener’s syn-
дроме etc., which affect either the mucus or ciliary beating; environmental con-
ditions (temperature, humidity); enzymatic degradation; immunity; and nasal
blood flow.

1. Disease state

The influences of diseased state on nasal bioavailability of drug product have not
been studied much. The most common and most frequent disease associated with
nose is rhinitis which is classified as allergic rhinitis and common cold. Allergic
rhinitis is characterized by hypersecretion, itching sneezing. In allergic rhinitis the
epithelial surface is damaged due to infection and inflammation of sinusseps.
The epithelial damage, abundant increase in the mucous secretion and high vascular
permeability associated with viral rhinitis are hypothetically favourable for nasal
drug absorption; however introduction of nasal dosage form as an external stimu-
lus increase “the nasal mucosa secretion and leads to drainage of dosage form and
hence reduce” the bioavailability of the drug[32].

2. Mucociliary clearance

The absorption of drugs is influenced by the residence (contact) time between the
drug and the epithelial tissue. The mucociliary clearance is inversely related to the
residence time and therefore inversely proportional to the absorption of drugs
administered. A prolonged residence time in the nasal cavity may be achieved by
using bioadhesive polymers, microspheres, chitosan or by increasing the viscosity
of the formulation.

Nasal mucociliary clearance can also be stimulated or inhibited by drugs, excipi-
ents, preservatives and/or absorption enhancers and thus affect drug delivery to
the absorption site. [13]

ABSORPTION ENHANCERS IN DRUG DELIVERY

As their name implies, absorption enhancer are used to improve absorption across the
nasal membrane. There are number of ways in which they can act: they may help solubilise or stabilise the drug; they may alter the properties of the mucous
layer, by opening tight junction between the cells; or they may increase membrane
fluidity [33]. Generally, the absorption enhancers act via one of the following
mechanisms [34]:
- Inhibit enzyme activity;
- Reduce mucus viscosity or elasticity;
- Decrease mucociliary clearance;
- Open tight junctions; and
- Solubilize or stabilize the drug.

Absorption enhancers are generally classified as physical and chemical enhancers.
Chemical enhancers act by destructing the nasal mcosa very often in an irrevers-
ible way, whereas physical enhancers affect nasal clearance reversibly by forming
a gel. The enhancing effect continues until the gel is swallowed. Examples of
chemical enhancers are chelating agents, fatty acids, bile acid salts, surfactants, and
preservatives. Osmolarity and pH may accelerate the enhancing effect [35].

MUCAADHESIVE POLYMERS IN DRUG DELIVERY

The mucoadhesive polymers are used as a means of delivery of therapeutically
active drugs including, vaccine, peptide, and protein via mucus membrane. A
bioadhesive materials have been defined as, a synthetic or biological material that
is capable of adhering to a biological substrate or tissue.
Mucosal drug delivery system localize the drug at a desired site and are therefore considered a better approach to design drug delivery system to organ like the buccal, nasal and vaginal cavity[6, 12]. System for mucosal drug delivery can be based upon its origin that may be natural or synthetic, the type of mucosa on which they attach like nasal, buccal, ocular or may be based up on their chemical structure, apart from these here we devise the mucosal drug delivery system on the basis of mechanism of binding – Non-covalent binding polymer and covalent binding polymer.

A. NON-COVALENT BINDING POLYMER

1. Anionic polymer
   In this group of polymer mainly COOH group is responsible for the adhesion to mucous gel layer like Carbopol, polyacrylate and their crosslinked modification.

2. Cationic polymer
   The strong mucoadhesiion of cationic polymer can be defined by ionic interaction between these polymer and anionic substructure such as sialic acid moieties of mucous gel layer. The swelling behaviour of this kind of polymer depends strongly upon pH and their swelling behaviour can be improved at higher proton concentration. These kinds of polymer are – Chitosan and polylysine etc.

3. Non ionic polymer
   Mucoadhesiveness of anionic as well as cationic polymer depend upon the pH value of the surrounding fluid while nonionic polymer is independent of pH value of surrounding fluid. Non-ionic polymers are not influenced by electrolytes of the surrounding milieu. Some of example of this kind of polymer are – Hydroxypropylcellulose, Hydroxypropylmethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone.

   a. Amphipic polymer
      The amphipic polymer shows cationic as well as anionic substructure on their polymer chain. The cationic polymer contain negative and the anionic polymer contain positive charge on site, the combination of positive as well as negative charge on the same polymer however seems to be compensate ionic interaction by this the cohesiveness of delivery system can be strongly improved.

B. Covalet Binding Polymer
   Some of the thiolated polymers have been synthesized. This may be anionic or cationic in nature shows strongly improved mucoadhesive properties as compared to the corresponding unmodified basis polymer are known as covalent binding polymer [17].

MUCAADHESIVE FORMULATION

A. Gel Formulations –
   These are high-viscous thickened formulation, those are prepared in the form of solutions or suspensions that used to deliver drug via nose. 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. The use of gel formulation used to improve absorption and to mask the irritation associated with patient excipients and target delivery to mucosa for better absorption. The use of gel formulation used to improve absorption and to mask the irritation associated with patient excipients and target delivery to mucosa for better absorption. The use of gel formulation used to improve absorption and to mask the irritation associated with patient excipients and target delivery to mucosa for better absorption.

B. Particulate Delivery System
   The nano and microparticulate delivery system make possible the nasal delivery of dosage forms and provide the classical approach to improve the bioavailability of formulation. Other matrix systems are also used where the drug is dispersed in polymeric material. These particulate delivery system can be developed by different encapsulation technique like spray drying, emulsification solvent evaporation, inotropic gelation and phase separation non solvent addition[38, 40]. Microspheres those are used in nasal drug delivery are insoluble but absorb water into sphere matrix and resulting to swelling of spheres and formation of gel.

In case of particulate delivery system the drug is loaded via incorporation into matrix system and released by certain mechanism such as [41].

   • Release from particle surface.
   • Diffusion of drug from swollen polymer matrix.
   • Drug released through the erosion of polymer.

C. Nasal Powders
   When the formulation like solution and suspension dosage forms are not recommended due to lack of drug stability, the nasal powder are the optimal dosage forms because these are more stable than suspension. But they are rarely used because they tend to irritate the nasal tissue. However, a nasal powder form may be useful when active ingredient can’t be formulated as solution or as suspension. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system but nasal mucosa irritancy and metered dose delivery are some of the challenges for formulation scientists and device manufacturers [40].

FUTURE PERSPECTIVE
   Although major progress has been made regarding intranasal drug delivery, there is still a distinct lack of information regarding this important topic. The studies searching for this information are urgent due to the rapid increasing in the aging population and the number of patient with neurological diseases around the world. The following future studies may be of particular interest.

   First, it is essential to search for the mechanisms underlying the direct drug transport from nose –to-brain after intranasal drug delivery, particularly those mechanisms in humans.

   Second, methods for intranasal drug delivery to treat neurological diseases must be improved. Previous studies have been suggested potential pathways to further increase the efficacy of intranasal drug delivery. Third, it appears increasingly necessary to conduct clinical trials to determine if intranasal drug delivery may be used to treat neurological disorders, which has been distinctly insufficient. Further studies on this topic may suggest that utilizing intranasal drug delivery could be critical advance for establishing effective therapeutic strategies for neurological diseases.

CONCLUSION
   The nasal route has become one of the most studied routes non-invasive routes because it offers a vast surface area, a thin membrane structure and a rich vascularity. The nasal epithelia barrier constitutes an obstacle for the drugs larger than 1,000 Da. Therefore, it is difficult for macromolecules, particularly those which are hydrophilic, to pass through the nasal mucosa. Moreover, the enzymes present in the nasal mucosal membrane constitute a problem for the stability of macromolecules with a peptide and protein structure. Numerous strategies have been developed to improve the passage of macromolecules through the nasal mucosa. It also bypasses the BBB and delivers the drug directly into the CNS. It acts as an alternative to parenteral and oral route for delivery of some drugs. Taking into consideration the current research interest in nasal delivery and positive outcomes from the clinical trials throughout the world it would not be wrong to expect a wide range of nasal products reaching the market in the near future.

   Hopefully all the issues will be resolved soon and we may get the wide variety of nasal products very soon for disorders such as migraine, nausea, heart attack, Parkinson’s disease, diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis etc.

REFERENCES

1. Squier C.A. and Wertz P.W. Structure and Function of the Oral Mucosa and Implica-


