Recent trends in drug delivery systems: Intranasal drug delivery

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Nasal route of drug delivery is commonly known for treatment of local ailments like cold, cough, rhinitis etc. Recently, efforts have been made to deliver various drugs, especially peptides and proteins, through nasal route for systemic use; utilizing the principles and concepts of rate controlled drug delivery and various polymers and absorption promoters. Considering the large number of problems associated with oral, parenteral, rectal and other routes of drug administration and gradual increase in interest of pharmaceutical scientists towards exploring the possibilities of intranasal delivery of various drugs, this article aims at giving an insight into nasal cavity, consideration of factors affecting and strategies to improve drug absorption through nasal route, pharmaceutical dosage forms and delivery systems with examples of some peptides for intranasal delivery, its advantages and limitations.

Drugs are administered traditionally by oral and parenteral routes for systemic delivery. The gastrointestinal tract (GIT) is the major route of drug entry to the systemic circulation. However, for some drugs this route presents problems. The gastrointestinal tract presents a hostile environment; it contains enzymes, a wide range of pH conditions and varies in its composition depending upon the presence or absence of food. Those drugs which are susceptible to either acid hydrolysis or extensive metabolism in the liver may exhibit poor bioavailability when administered via this route. Drugs administered via the parenteral route gain access to the systemic circulation directly and produce maximum plasma levels but this route is associated with pain and discomfort and can only be given by medical personnel. Parenteral formulations need to be sterilised and this increases the cost. In addition certain health risks are associated with this route, e.g., psychological distress, occasional allergies and hypertrophy or atrophy of the subcutaneous fat at the injection site specially on chronic administration.

In an attempt to circumvent these problems, alternative routes of drug administration are being investigated. Transdermal, rectal, buccal and nasal routes bypass hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs. However, transdermal route does not provide rapid blood levels and is limited to controlled delivery of potent lipophillic drugs. The rectal route suffers from variable patient acceptance and depending upon the site of absorption the drug may be subjected to hepatic first-pass metabolism. Buccal and sublingual routes of drug administration are of much interest, but sometimes pose inconveniences during speaking, eating and drinking.

Hence, the nasal route holds potential for administration of various drugs with avoidance of first-pass metabolism and the better bioavailability and therapeutic profiles. The nasal route for drugs administration has received the attention of mankind since ancient times. Nasal therapy (Nasasya karma) is a recognized form of treatment in the Indian system of medicine. The intranasal application of tobacco snuff, cocaine and various hallucinogenic and psychotropic agents has been known for a long time. It is therefore surprising that only in the past decade this route attracted much attention for systemic medication. The results till date indicate that the nasal route of drug delivery is considered to be the most promising due to its following potential advantages

1. Avoidance of drug degradation in the luminal fluid of the GIT.
2. Avoidance of hepatic first-pass metabolism in the liver or gut wall.
3. Easily accessible.
4. Rapid absorption and fast onset of action.
5. Suitable for administration for long term therapy.
Factors influencing nasal drug absorption

(A) Physicalchemical

(a) Molecular size and structure—Nasal absorption decreases significantly when molecular weight of drug is greater than 1000 Daltons. A reverse relationship has been demonstrated between molecular size and the nasal absorption in rats and rabbits. These studies support the idea that water soluble, high molecular weight drugs cross the nasal mucosa mainly by passive diffusion through the aqueous pores (i.e., tight junctions). Supporting evidence is given by McMartin et al. who looked for relationships between published value for nasal absorption of a large variety of peptides and proteins and their physicochemical properties. The best correlation exists between molecular size and extent of nasal absorption, consistent with diffusion through intercellular pores as a major mechanism of transport for peptides and proteins. Data on active transport of peptides by endocytosis are scarce. It is interesting to note that earlier reports on relationship between molecular weight and nasal absorption of peptides and proteins are very contradictory. Some authors claim an inverse relationship between molecular size and nasal bioavailability whereas others state that such relationship does not exist. Apparently, the nasal absorption of peptides and proteins is rather complicated due to variously charged and variously shaped molecules. The effect of molecular weight on absorption is related to the effective size of the molecules. Cyclic peptides are absorbed much better than linear ones.

(b) Hydrophilicity/Lipophilicity—The effect of drug hydrophilicity on absorption rate has been clearly shown by Carbo et al. using progesterone as a model drug. The systemic bioavailability was decreased with increasing hydrophilicity of the drug.

(B) Biochemical and physiological

The nasal mucosa is by itself an enzymatic barrier to nasally administered drugs consisting of several different proteolytic/hydrolytic enzymes. The enzymes present are both oxidative (e.g., cytochrome p-450, aldehyde dehydrogenase, carboxylesterase, carboxic anhydrase) and conjugative (e.g., glucuronate sulphate and glutathione transferases) enzymes. Cytochrome P-450 activity in the olfactory region of the nasal cavity is even higher than in the liver. The enzymatic activities clearing peptides and proteins are exo- and endopeptidases (e.g., aminopeptidases, carboxypeptidases, trypsin like activities, cathespin), which are present at the surface of the nasal mucosa or within epithelial
cells. Among these enzymes, aminopeptidase activity is predominant. The nasal and ileal mucosal homogenates from the albino rabbit showed similar aminopeptidase activities when measured at a protein concentration of approximately 10 mg/ml \(^1\). The enzymatic barrier characteristics of the nasal mucosa create "a pseudo-first-pass-effect" which may hamper nasal drug absorption \(^{16}\).

**C) Nasal mucociliary clearance**

It is an important physiological defence mechanism of the nose to protect the body against the inhalation of foreign substances. Inhaled/instilled particles are cleared from the nasal cavity by mucociliary clearance. Thus every pharmaceutical system intended for intranasal use will interact with the nasal clearance mechanism. Ciliostasis prevents the defensive barrier from functioning properly. Consequently, as ciliary beating is the most important parameter in nasal mucociliary clearance, it should not be affected by nasal medication and additives such as preservatives and absorption enhancers. Furthermore, the rheological properties of the mucus layer can change after contact with pharmaceutical formulations. This will certainly affect the clearance and exposure of drugs to the mucosa. To study the action of drugs, additives and pharmaceutical dosage forms on mucociliary clearance, measurement of mucus transport time (MTT) and ciliary beat frequency (CBF) are currently used.

**D) Common cold or pathological conditions**

The common cold or any pathological conditions involving mucociliary dysfunction can greatly affect the rate of nasal clearance and subsequently the therapeutic efficacy of drug administered intranasally. Nasal obstruction as a result of extensive nasal polyposis would reduce the capacity of nasal absorption \(^{18}\). In addition, atrophic rhinitis or severe vasomotor rhinitis could also reduce the usefulness of the nose to absorb a drug. In some people, an excessive response of the secretory system to some irritants could drain away whatever is introduced prior to its absorption. Such tendency may exist in persons with severe nasal allergies. Nevertheless, it has been shown that the common cold and rhinitis do not decrease the bioavailability of buserelin \(^{19}\) and desmopressin \(^{20}\).

**E) Pharmaceutical**

(a) **Formulation (pH and osmolarity)**—The formulation plays an important role in the nasal absorption of drugs as it does in case of other routes of administration. The influence of pH and osmolarity on the nasal absorption of secretin are studied in rats \(^{21}\). The study indicated that the absorption of secretin increased linearly as pH decreased from 7.0 to 2.94. Its bioavailability was also affected by sodium chloride concentration in the formulation. The maximum absorption was obtained with a hyperosmolar saline solution of 0.462M.

(b) **Droplet size**—The mean flow rate of the mucociliary system of the normal nose is about 5 mm/min, upto 20 mm/min \(^{22}\) or administered drugs are cleared from the nasal cavity within 15 to 20 min, depending on the particle size of the materials and the site of deposition. The particles with an aerodynamic size above 10-20 μm are all deposited in the nasal cavity, whereas particles smaller than 1 μm pass with inspired air into the lungs.

(c) **Site of deposition**—However, the degree of absorption also depends on the site of deposition of nasally administered substances which depends on the delivery system and the technique of administration. For instance, the deposition and clearance of nasal sprays and nasal drops of Tc-99m labeled human serum albumin were studied \(^{23}\) in humans using gamma scintigraphy. The nasal spray was deposited mainly in the anterior part of the nose whereas the nasal drops dispersed more extensively in the nasal cavity. The solution deposited from the nasal drops cleared more rapidly than from the nasal spray.

(d) **Delivery system**—Various delivery systems such as nasal sprays, nasal drops, cotton pledget, insufflator, nasal insert and nasal jelly are currently used for administration of drugs through the nasal cavity. The different delivery efficiency of these systems affect the site of deposition and the degree of absorption.

(e) **Drug distribution**—Drug distribution in the nasal cavity is another important factor in the nasal absorption of drugs. This in turn is affected by several factors such as:

(i) **Area of the nasal mucous membrane exposed**—An ointment containing 40mg progester-
one when applied into both the nostrils of a woman showed increased bioavailability compared to that obtained after administration to just one nostril.  

(ii) Volume of solution applied—Application of a large volume of a solution from the nasal drop bottle gives a good distribution over the nasal cavity, whereas samill volume gives unsatisfactory results.  

(iii) Types of nasal delivery systems—Various nasal delivery systems such as drop bottles, plastic bottle nebuliser, atomised pump and metered dose pressurised aerosol showed significant differences in drug distribution in human nose. The study has shown that the relative bioavailability and biological response to nasal desmopressin was better with nasal spray than with nasal drops because of better distribution. For a pressurised aerosol system, dosage should be delivered twice in each nostril, i.e., one puff in the upper direction and one puff in the lower direction, in order to yield a reasonably good distribution of drug.

**Strategies to improve nasal absorption**  
Though the nasal absorption of small non-peptide drugs is considerably good, the nasal bioavailability of peptide and protein drugs is low. The low nasal absorption may be due to poor membrane permeability to larger molecules or lack of lipophilicity or metabolic degradation by aminopeptidase present in the nasal mucosa. To overcome these problems several strategies have been tried to enhance the nasal absorption of peptides and protein drugs to improve their bioavailability.

(1) Synthesis of stabilised and more lipophilic analogues  
Many potent peptide analogues have been synthesized which possess high lipophilicity and increased stability to enzymatic degradation. This approach has led to the development of many nasally active peptides for example, metkephamid, antidiuretic drug desmopressin, LHRH agonist buserelin, leuproide and nafarelin. The effect of these nasally administered LHRH analogues on the induction of ovulation is increased to 50-200 times in comparison to the parent compound LHRH, but their nasal bioavailability remained very low (2-3%). The discrepancy found between nasal bioavailability and induced biological activities can probably be attributed to high affinity of the pituitary receptors for these LHRH agonists.

(2) Peptidase and protease inhibitors  
The nasal epithelial tissue contains substantial amounts of peptidases and proteases. These enzymes are able to degrade peptides and proteins like enkephalins, insulin and proinsulin. The predominant enzyme present is aminopeptidase. The aminopeptidase inhibitors such as bacitracin, bestatin and amastatin have been found to promote the nasal absorption of LHRH peptides, salmon calcitonin, leucine enkephalin and human growth hormone in rats. A new aminopeptidase inhibitor, boroleucine has also been found to remarkably enhance the nasal absorption of leucine enkephalin in rats. The intranasal use of α-aminoboronic acid derivatives for the stabilization of externally administered leucine-enkephalin as a model peptide was studied in situ in rats. These compounds were found to greatly inhibit the degradation of leucine enkephalin in the nasal perfusate. Enzyme inhibition was greater with boroleucine and borovaline than with borotaloline derivatives. The boroleucine derivatives was more than 100 times more effective in enzyme inhibition than bestatin and more than 1000 times more effective than puromycin.

(3) Absorption enhancers  
Absorption enhancers have most frequently been used to improve the bioavailability of intranasally administered peptides and proteins. Various types of absorption enhancers along with examples are presented below:  

<table>
<thead>
<tr>
<th>Class</th>
<th>Compounds</th>
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<tbody>
<tr>
<td>(a) Surfactants</td>
<td>Polyoxyethylene-9-lauryl ether (laureth-9)</td>
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<tr>
<td>(b) Glycosides</td>
<td>Saponins</td>
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<tr>
<td>(c) Bile Salts</td>
<td>Dihydroxy Salts</td>
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<td></td>
<td>Sodium deoxycholate</td>
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<td>Sodium glycodeoxycholate</td>
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<td>Sodium taurodeoxycholate</td>
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<td>Trihydroxy Salts</td>
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<td>Sodium cholate</td>
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<td>Sodium glycocholate</td>
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<td></td>
<td>Sodium taurocholate</td>
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Mechanism of action of absorption enhancers

1. Increase in membrane fluidity either by creating disorder in the phospholipid domain in the membrane or by facilitating the leaching of drugs from the membrane.

2. Decrease in viscosity of mucus layer thereby increasing membrane permeability.

3. Inhibit proteolytic enzymes at the absorption site.

4. Transient loosening of the tight junctions between certain epithelial cells.

5. Increase paracellular or transcellular transport.


7. Initiate membrane pore formation.

8. Increase nasal blood flow, thereby raising the concentration gradient across the nasal mucosa.

Hermens and coworkers have found that all enhancers have a ciliostatic/toxic effect. However, all the data available today indicate that sodium taurodihydrofusidate (STDF) is one of the most promising enhancers system.

The most important drawback for the use of chemical nasal enhancers is the possibility of toxic side effects. The chronic administration causes irreversible damages to the nasal mucosa. There is presently a need for good nasal absorption enhancers with low or free of any side effects.

**Intranasal administration of peptides**

The nasal administration of peptide hormone has been attempted previously notably with insulin in the early 1920s. The nasal administration of peptides has since become routine for peptides like vasopressin and its analogues (for the management of diabetes insipidus), LHRH (for the management of cryptorchidism) and its highly active analogues (buserelin, leuprolide, LHRHt, and nafarelin, for the management of prostate carcinoma, mammary carcinoma, uterine leiomyoma, endometriosis, precocious puberty and for contraception) and oxytocin (for labor induction). All these peptides consist of either 10 amino acids or less and therefore possess relatively good permeability across nasal mucosal membrane.

Intranasal administration of some common peptides with their therapeutic benefits are presented below:

**Calcitonin**—Calcitonin, a polypeptide hormone, lowers blood calcium concentration and inhibits...
bone sorption. It is currently used for the treatment of several bone diseases such as hypercalcemia, postmenopausal osteoporosis and pagets disease. Calcitonin is presently given either as subcutaneous (s.c.) or intramuscular (i.m.) injection daily or on alternate days for prolonged periods. Nasal administration of calcitonin has been examined\textsuperscript{46-48} clinically with different dosage forms and formulations.

A two year study on efficacy and safety of nasal calcitonin suggests that calcitonin nasal spray has a significant bone protective action\textsuperscript{49}. Clinical studies have demonstrated that nasal delivery of calcitonin is both convenient and reliable.

Human calcitonin is absorbed through the nasal mucosa without use of surfactants\textsuperscript{46}. The bioavailability is 1/14 times to that of s.c. calcitonin. However, the presence of surfactants such as TDHF and sodium glycocholate enhanced the bioavailability 6-7 times when compared to formulations with no surfactants\textsuperscript{46}.

\textbf{Insulin}—Insulin is a protein hormone with a molecular weight of about 5800. The treatment of diabetic patients with insulin requires daily subcutaneous injections. For both type I and II diabetes, these insulin injections cause local discomfort and inconvenience. More importantly, the subcutaneous insulin therapy is limited by the delayed onset time and time to reach maximum plasma concentration (T\textsubscript{max}). Furthermore, the injected insulin can not be adjusted to changing requirements during exercise or meals and therefore can cause large inter and intra subject variability which can result hyper or hypoglycemia.

To date it has been clearly shown that nasal delivery of insulin results in rapid peaks of circulating insulin which controls meal induced hyperglycemia. The rapid onset of insulin action simulates the release of insulin by the normal pancreas, at least in timing. In contrast, the delay in absorption from the subcutaneous site may permit hyperglycemia to occur. However, only the i.v. and i.p. injections of insulin administered at meal time controls the meal induced glycemic excursion. As a result, nasal delivery has been advocated as a potentially useful alternative to s.c. insulin for meal time insulin therapy.

The modern era of intranasal (i.n.) insulin administration began in the early 1980s. Insulin was only moderately absorbed when the pH of the solution was lowered to about 3.5 or when surfactants like bile salts, PEG, detergents, saponin, polyethers usually at 1% w/v concentration were used in the formulations.

Using intranasal drops of soluble insulin (0.9U/kg) with 1% sodium glycocholate Pontiroli \textit{et al.}\textsuperscript{51} demonstrated a decrease of blood glucose levels and appearance of insulin in blood stream, both in normal subjects and in patients with type-I diabetes. The efficiency was about 1/9 times to that of intravenous insulin. The bioavailability of intranasal insulin can be improved by increasing the sodium glycocholate concentration from 1-4% (Pontiroli \textit{et al.})\textsuperscript{52}. Longenecker\textsuperscript{53} used TDHF as absorption enhancer and found high reproducibility of intranasal insulin. Previous studies have shown that chemically modified cyclodextrins, especially the methylated derivatives, are more potent enhancers of nasal insulin absorption, than the parent cyclodextrins\textsuperscript{54-56}. The absorption enhancement afforded by the methylated cyclodextrins can be attributed primarily to their ability to reduce the barrier function of the nasal mucosa and to protect insulin against proteolysis\textsuperscript{55}. Shao \textit{et al.}\textsuperscript{57} demonstrated that cyclodextrins inhibit the self association of insulin into oligomers thus making insulin more available for insulin absorption.

DS-1 is a semisynthetic derivative of QS-21, a natural saponin isolated from the bark of the \textit{Quillaja saponaria} Molina tree. It promotes the systemic absorption of aminoglycoside antibiotic when used nasally to mice and rats\textsuperscript{57} and insulin when applied topically to the rat eye or nose even at concentration as low as 0.025\% \textsuperscript{58}. No other absorption enhancing agent has been this effective when used at such low concentrations. The hypoglycemic response was more rapid in onset and more transient than that observed when insulin was injected (s.c.).

The effect of soyabean-derived sterol mixture (SS) and its glucoside mixture (SG) as an enhancer to improve the nasal bioavailability of insulin is reported in rabbits\textsuperscript{59}. SG possesses excellent properties in peanut oil suspension as an enhancer and is superior to the known absorption enhancers.

\textit{Illum et al.}\textsuperscript{60} reported the successful use of a medium molecular weight chitosan to enhance the nasal absorption of insulin in rat and sheep models.
The mechanism of action was suggested to be a combination of bioadhesion and transient widening of the tight junctions in the nasal membrane. Recently, a range of chitosans differing in molecular weight and degree of deacetylation, were all shown to enhance the systemic delivery of insulin when administered nasally to rats. Further, it was shown that the chitosan caused no membrane or cellular damage in rat nasal perfusion model and only a transient decrease in mucociliary transport velocity in the frog palate model. It is also reported that hyaluronic acid ester microspheres significantly enhance the intranasal absorption of insulin in sheep.

**Endocrine hormones**

**Human Growth Hormone (hGH)—** A protein hormone, is currently administered s.c. or i.m. to children deficient in growth hormone for treatment of hypopituitary dwarfism. More recently hGH was reported to reverse the biological effects associated with aging.

The nasal bioavailability of recombinant methionyl-human growth hormone (Met-hGH) was found to be less than 1% as compared to i.v. administration. However, in presence of absorption enhancer sodium glycocholate, the nasal absorption of Met-hGH was increased to about 7-8%. The nasal absorption of hGH in the presence of lyophosphatidyl choline and sodium dihydrofusidate derivatives was investigated in rats, rabbits and sheep and it has been found that these absorption enhancers significantly improves delivery of hGH.

**Luteinizing Hormone Releasing Hormone (LHRH)—** LHRH, a decapeptide secreted in the hypothalamus stimulates the release of gonadotropins, LHRH and follicle stimulating hormone (FSH), from the anterior pituitary. In recent years, potent LHRH agonist analogues have been developed. These analogues suppress gonadotropin release for treatment of endometriosis, prostate carcinoma and female contraception. These hormones are essentially inactive when administered orally.

The nasal bioavailability of LHRH was estimated to be approximately 1% when compared with peak plasma levels of LHRH after i.v. administration. The treatment of cryptorchidism in young boys requires injections and it is not well tolerated by infants. In some cases, it leads to symptoms of androgenic stimulation which are unwanted in prepubertal children. The nasal administration of LHRH has been found to be effective with a multiple dosage regimen. Although a higher nasal dose is required than the i.v. dose, this route seems a safe and convenient for LHRH administration. Moreover absorption is not affected by common cold or intercurrent rhinitis. **LHRH agonist (buserelin),** a synthetic non peptide buserelin acetate is a highly potent agonist of LHRH. In contrast to acute dosing, the long term treatment with the LHRH agonist paradoxically desensitizes the pituitary gonadal system, leading to a reversible biochemical castration. This paradoxical effect is successfully utilized in the treatment of hormonally sensitive disorders such as endometriosis, precocious puberty and leiomyoma. Because of the low oral bioavailability of buserelin, it is administered via the intranasal route or by s.c. implants or microparticle injections.

The effects of chemically modified cyclodextrins on the nasal absorption of buserelin, agonist of LHRH were investigated in anaesthetised rats. α-cyclodextrins, dimethyl-α-cyclodextrins and dimethyl-β-cyclodextrins significantly enhanced the rate and extent of nasal bioavailability of buserelin with the efficacy increasing in the order α-cyclodextrin <dimethyl-α-cyclodextrin <dimethyl-β-cyclodextrin. In particular, DM-β-cyclodextrin improved the nasal bioavailability of buserelin about four fold, reaching ~60% when compared to i.v. administration. **Cyclodextrins** protect the buserelin acetate from proteolytic enzymes by including the aromatic amino acid within their intramolecular cavity. Cyclodextrins are ca-
pable of extracting specific membrane lipids such as cholesterol and phospholipid from the nasal mucosa through rapid and reversible formation of inclusion complexes. This selective solubilisation of the membrane lipids may reduce the barrier function of the nasal epithelium.

Nasal absorption of nafarelin acetate, a potent LHRH agonist, in rhesus monkeys was found to be rapid and reproducible \(^{33}\). Clinical trials of nasal delivery of nafarelin have shown good efficacy in the treatment of endometriosis and it is currently marketed in the United States.

The research has also now been initiated on a novel peptide absorption promoting agents which are termed as "physiological modifying agents". These agents have vasoactive properties and exert their action by increasing nasal mucosal blood flow. As a result the concentration of the drug on the basal side of the nasal mucosal membrane will remain low, leading to an increase in effective concentration gradient and thereby augmenting peptide permeation across the mucosal membrane by passive diffusion.

Agents capable of increasing nasal blood flow are histamine\(^ {21}\), leukotriene D\(_4\)\(^ {27}\), prostaglandin E\(_2\)\(^ {23}\), \(\beta\)-adrenergic agonists, isoprenaline and terbutaline\(^ {24}\). Also included in this category are agents which promote the release of endogenous vasoactive substances such as histamines, Kinins, prostaglandins and vasoactive peptides. Carboxymethyl cellulose (CMC), a bioadhesive agent and histamine, a vasodilator were used to enhance the intranasal absorption of desmopressin, a 9-amino acid vasopressin analog in human trials\(^ {25}\). The intranasal administration of histamine immediately prior to desmopressin significantly increased nasal blood flow response, suppressed urine volume flow for longer duration, and increased urine osmolality, electrolyte and creatinine concentration. The increase in duration of activity was consistent with increased transnasal absorption of the peptide.

**Pharmaceutical formulations**

The fourth strategy for improved delivery of peptides and proteins through nasal route is formulation approach. Rapid mucociliary clearance of drugs from absorption sites in the nasal cavity is responsible for low bioavailability. With the aim to prolong the nasal residence time and improve the absorption efficiency, remarkable progress has been reported with the formulation approach.

**Various dosage forms**

The conventional nasal dosage forms are simple solutions meant for local application. These solution dosage forms are effective in relieving the symptoms of rhinitis and common cold by providing better distribution of the drug than any other dosage form. However, for systemic medications a satisfactory pharmacokinetic profile and good bioavailability are essential.

Since solution dosage forms are easily subjected to nasal mucociliary clearance, other dosage forms such as suspensions, powders and inserts are developed to improve the nasal drug absorption into the systemic circulation, e.g., the nasal absorption of human sodium insulin was found\(^ {26}\) to be better from suspensions when compared to solution dosage forms. This might be due to higher drug concentration on nasal membrane which in turn results in an increased concentration gradient for drug diffusion.

The powder dosage form is prepared by mixing the drug with water-soluble, water-dispersible or water-insoluble polymers. The mixed powder is dissolved and lyophilized and filled in hard gelatin capsule. The powder dosage form can be administered with an insufflator or other delivery devices.

**Gel formulations**—The nasal absorption of nifedipine from various gel formulations was investigated in rats\(^ {27}\). Using Polyethylene glycol (PEG) as a base, both absorption and elimination of nifedipine was rapid. However, when a mixture of PEG and carbopol were used as a base, a relatively high nifedipine concentration and a prolonged action were observed. These data suggest that nasal absorption can be considerably improved by choosing appropriate excipients and optimising the formulation.

**Sprays vs drops**—Nasal spray deposit more anteriorly, resulting in slow clearance of sprays than of drops. The nasal bioavailability of desmopressin has been found to be significantly increased following spray administration as compared to nasal drops\(^ {27}\). The clearance of nasal formulation can be influenced by viscosity of the preparation. The clearance half life \((t_{1/2})\) of the nasal spray solutions
containing HPMC increased with increasing concentration of the viscous agents.

**Powder vs solution**—Powder dosage forms of peptides and proteins offer advantages over liquid formulation. In powder form the chemical stability of the drug is usually increased, preservatives in the formulation is not required, and it is possible to administer larger amounts of drugs and excipients. Intranasal delivery of a nafarelin powder dosage form with high molecular weight dextrans provided a higher peptide absorption than a liquid formulation. A clinical study comparing the administration of powder and solutions of glucagon and human calcitonin with dihydrofusidate as enhancer through nasal route indicated the powder formulations were as effective as the spray solutions. In another study, it was reported that in rabbits nasal powder dosage forms of salmon calcitonin were twice as effective as solutions.

### Bioadhesive as nasal delivery systems

To reduce the nasal clearance and improve the nasal drug absorption, bioadhesives were introduced in nasal drug delivery. These systems utilised bioadhesive gels or microspheres. The powder dosage form of insulin mixed with several bioadhesive excipients such as crystalline cellulose, hydroxypropyl cellulose and neutralized carbopol 934, showed different degrees of enhanced nasal absorption of insulin in dog. The absorption of insulin from the nasal mucosa was fastest in the preparation with crystalline cellulose and was sustained in the preparation with neutralized carbopol 934. A system composed of insulin and CP 934 freeze dried together prior to mixing with crystalline cellulose, resulted in the most efficient enhancement of nasal absorption. A polyacrylic acid gel bioadhesive system improved the absorption of insulin and calcitonin in rats.

The microspheres form a gel-like layer which is cleared slowly from the nasal cavity, resulting in prolonged residence time of the drug formulations. An increased contact time would possibly increased the absorption efficiency of the drug. Bioadhesive microspheres containing materials such as starch, albumin and dextran with particle sizes of 40-60 μm have been found to be cleared from the nasal cavity much slower than solutions and powder preparations. The absorption enhancement by starch microspheres is not only related to their mucoadhesive properties, but also to their own inherent absorption-promoting effect by widening the spaces between the tight junctions. Insulin and starch microspheres administered nasally to rats resulting in rapid decrease in blood glucose levels. Nasal bioavailability was found to be 30% when compared to i.v. dose.

### Limitations of nasal drug delivery systems

1. Nasal cavity provides smaller absorption surface area when compared to GIT.
2. Low bioavailability of large proteins.
3. Histological toxicity of absorption enhancers used in nasal drug delivery is not yet clearly established.
4. Nasal irritation leads to inconvenience.
5. Question of untoward immunogenic effects from molecules arising with nasal delivery systems.
6. The route is adversely affected by local disorders such as rhinitis and pathophysiological changes.
7. Large interspecies differences in nasal drug absorption.

During pharmacokinetic and formulation studies of nasally administered drug severe limitations in the interpretation of the results may occur. Firstly, intramodel differences appear to exist (anaesthetised versus conscious animals). Secondly, large interspecies differences in the nasal absorption of certain drugs have been found. The anaesthetised rat model by Hirai et al. is widely employed for studying transport across the nasal mucosa. But rabbits, dogs, sheep and monkeys are also frequently used to investigate nasal drug absorption in vivo. It is difficult to compare studies using different animal models due to variations in experimental conditions and dosage forms. Nasal peptide and protein absorption vary considerably, depending on the drug and absorption enhancer used.

### Conclusion

The nose is a complex organ with multiple functions. The nasal cavity provides a highly vascularised surface of the nasal mucosa for the absorption of drugs. The main advantages of the nasal route of administration are that the drug degradation in the gastrointestinal tract is eliminated,
hepatic first-pass metabolism is avoided and absorption of drugs and onset of action can be achieved rapidly. The absorption of small drug molecules through nasal route appears satisfactory, and yields relatively good bioavailability. Nasal absorption of peptides is an attractive option but it has many drawbacks, e.g., low bioavailability, local irritation and toxicity on long term use. A bioavailability of 1-2% for an expensive recombinant peptide is not acceptable because of high cost associated with the treatment. Therefore, it is necessary to find a biocompatible absorption promoter.

The proposed promoters act by different mechanisms either separately or jointly. They may alter the mucus layer, inhibit proteases in the nasal mucosa, increase the membrane fluidity, widen the tight junctions, etc. However, a major drawback with all these enhancers is their local irritation and toxicity on the nasal mucosa. Furthermore, the immunological consequences of nasal administration of peptides have also to be investigated, especially the local immunization and production of IgA which can induce inflammatory reactions and prevent absorption of biologically active peptides. The efficacy of the enhancers in nasal drug absorption has been shown to be greatly dependent on interspecies and experimental animal model differences. It is therefore advisable to perform human experiments at an early stage in the development of those nasal formulations which contain selective and safe absorption enhancers.

In particular, the nasal delivery of peptides and proteins is a promising alternative to injectable route of administration. It is very likely that in the near future more drugs will come in the market intended for systemic absorption in the form of nasal formulations.

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