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INTRANASAL DRUG DELIVERY SYSTEMS; AN OVERVIEW

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THERAPY through intranasal administration has been an accepted form of treatment in the Ayurvedic System of Indian Medicine. In recent years, many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Advances in biotechnology have made available a large number of protein and peptide drugs for the treatment of a variety of diseases. These drugs are unsuitable for oral administration because they are significantly degraded in the gastrointestinal tract or considerably metabolised by first-pass effect in the liver. Even the parenteral route is inconvenient for long term therapy. Of many alternate routes tried, intranasal drug delivery is found much promising for administration of these drugs[1,2]. In this article, an overview on the design and development of intranasal drug delivery systems is presented.

PHYSIOLOGY OF THE NOSE FOR DRUG DELIVERY:

The nasal passage which runs from the nostrils to the nasopharynx has a length of approximately 12 to 14 cm. The nasal mucosa is composed primarily of pseudostratified ciliated columnar epithelium, which because of the presence of microvilli, has a large surface area available for drug absorption[3]. The tissue is highly vascularised and provides ready access to the circulatory system while avoiding first-pass metabolism by the liver.

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The nasal epithelium is covered with a mucus layer. The blanket of nasal mucus is transported in a posterior direction by the synchronised beat of the cilia. The velocity of the mucus transport is about 8 mm/min. The particles entrapped in the mucus layer are transported with it and thereby effectively cleared from the nasal cavity. The combined action of mucus layer and cilia is called mucociliary clearance. Nasal secretions in adults have a pH in the range of 5.5 to 6.5 and often contain a variety of enzymes. The enzymes present are both oxidative (cytochrome. P-450, aldehyde dehydrogenase, carboxyesterase, carbonic anhydrase), and conjugative (glucuronyl transferase and glutathione transferase). The existence of aqueous pores or channels in the nasal mucosa was speculated through which water soluble drugs permeate[4]. The unionised lipophilic drugs cross the nasal epithelial barrier through the transcellular route.

NASAL DELIVERY OF DRUGS FOR SYSTEMIC MEDICATION:

Systemic absorption from nasal cavity has been described for several drugs including scopolamine, hydralazine, propranolol, insulin, butorphanol, enkephalins, buprenorphine, dobutamine, human growth hormone (hGH), calcitonin, leutinizing hormone- releasing hormone (LHRH) and estradiol[1].

Butorphanol tartrate is a potent analgesic with an excellent safety profile. Because of the rapid hepatic first-pass metabolism, currently it is manufactured as a parenteral dosage form. However, it has been recently reported that nasal butorphanol pro-

vided rapid onset of analgesia with no evidence of local irritation[5].

Buprenorphine is a potent and long acting synthetic opiate analgesic. In rats the nasal bioavailability was found to be 97% of that found after intravenous administration whereas, its intraduodenal availability was only 9.8%[6]. This data indicate intranasal delivery as an alternate route to parenteral administration of buprenorphine.

Dobutamine (β-1 adrenergic agonist) is a selective positive ionotropic drug. Because of the short plasma half-life of 1-2 minutes, the clinical utility of dobutamine is currently limited to IV infusion. Nevertheless, it has been documented that the intranasal dobutamine in dogs and rats showed increased bioavailability over intravenous administration[7].

The intranasal absorption of recombinant **methionyl human growth hormone** and **hGH** was studied in animal models[8,9]. The presence of an absorption enhancer increased the intranasal bioavailability of these growth hormones significantly.

Calcitonin, a polypeptide hormone, is currently administered subcutaneously or intramuscularly for the treatment of several bone diseases for prolonged periods. Controlled clinical studies have demonstrated the nasal delivery of calcitonin to be reliable and convenient[10,11]. Nasal formulation of calcitonin is being currently marketed in Europe.

Though many studies[12-14] have demonstrated intranasal delivery as an alternative to subcutaneous **insulin** for mealtime insulin therapy, insufficient bioavailability and safety aspects of absorption enhancers remain as limitations.

Intranasal administration of **propranolol** led to a bioavailability quite comparable to intravenous administration[15]. Higher concentrations of **estradiol** and **progesterone** were observed in the C.S.F. following treatment with a nasal spray than those after i.v. injection[16].

FACTORS AFFECTING THE NASAL ABSORPTION OF DRUGS:

The nasal absorption of drugs is influenced by physiological, physicochemical and pharmaceutical factors.

PHYSIOLOGICAL FACTORS : The nasal mucociliary clearance is from 5mm/min to 20mm/min in humans[17]. Hence under normal conditions the administered drugs are cleared from the nasal cavity within 15 to 20 minutes depending on the size of drug particles and the site of deposition.

Drug particles with a size of less than 1μm pass with the inspired air into the lungs whereas those with a size in range of 10-20 μm are nearly all deposited in the nasal cavity. The site of drug deposition depends on the delivery system and the technique of administration. This is evident from the studies carried out by Hardy *et al* in humans[18].

The effect of aminopeptidases present in the nasal mucosa is to be considered in the absorption of peptide and protein drugs. *In vitro* studies[17,19] using nasal mucosal homogenates provide useful information to assess the degradation of a specific peptide-protein drug.

The common cold or any pathological conditions involving mucociliary dysfunction can greatly affect the rate of nasal clearance and subsequently the therapeutic efficacy of drugs administered intranasally. Nasal polyposis, atrophic rhinitis and severe vasomotor rhinitis reduced the capacity of nasal absorption of a peptide drug, cerulein (LHRH agonist)[20].

While considering the intranasal delivery of peptide drugs one must not forget the possibility of complexation by immunoglobulin (Ig) which leads to an increase in the molecular weight with resultant difficulty in crossing the biological membrane.

PHYSICOCHEMICAL FACTORS: The effect of pH on nasal absorption of benzoic acid was demonstrated[21]. About 44% of benzoic acid was ab-

sorbed at pH 2.5 (more unionised) whereas, only 13% was absorbed at pH 7.2.

The nasal absorption decreases sharply when the molecular weight is greater than 1000 daltons. The study carried out by Fisher *et al*[22] showed a good linear correlation between the amount of drug absorbed nasally and the molecular weight.

Lipophilicity is another important factor that influences the nasal absorption of drugs. It is usually represented by chloroform/water or octanol/water partition coefficient. But none of these methods provided a good correlation for the systemic availability of barbiturates[21] and progestational steroids[23]. Most probably the systemic availability of drugs through nasal cavity could be better correlated with nasal mucosa/buffer partition coefficient.

PHARMACEUTICAL FACTORS: The **formulation** plays as important a role in the nasal absorption of drugs as it does in case of other routes of administration. For example, the influence of pH and osmolarity on nasal absorption of secretin was studied in rats[24]. The study indicated that the nasal absorption of secretin increased linearly as the pH decreases from 7.0 to 2.9. Its bioavailability was also affected by the sodium chloride concentration in the formulation. Maximum absorption was obtained with a nasal solution containing 0.46 M sodium chloride. Morimoto *et al* studied the nasal absorption of nifedipine from various *gel* formulations in rats[25]. Using polyethyleneglycol (PEG) as a base, both absorption and elimination of nifedipine was rapid and with Carbopol as a base, the absorption was low. But with a mixture of PEG and Carbopol, a relatively high nifedipine concentration and prolonged action were observed. These data suggest that nasal absorption can be considerably improved by choosing appropriate excipients and optimising the formulation.

Various **delivery systems** such as nasal spray, nasal drops, cotton pledget, insufflator, nasal insert and nasal jelly are currently used for administration of drugs through nasal cavity. Of these, nasal spray was found[3,26] to be the most accurate in delivering the dose. However, the degree of drug absorption also depends on their site of deposition. This is clear from a study carried out by Hardy *et al*[18] where the nasal spray was deposited mainly in the anterior part of the nose and the nasal drops were dispersed more extensively in the nasal cavity. The solution deposited from nasal spray cleared slowly than from nasal drops.

Drug distribution in the nasal cavity is another important factor in the nasal absorption of drugs. This inturn is affected by several factors such as area of nasal mucus membrane exposed to drug molecules, volume of solution applied (in case of nasal drug solution) and type of nasal delivery systems. For example, an ointment containing 40 mg progesterone when applied into both the nostrils of a woman showed increased AUC compared to that obtained after administration to just one nostril[27]. Application of a large volume of a solution from the nasal drop bottle gave a good distribution over the nasal cavity, whereas, small volumes gave unsatisfactory results. Various nasal delivery systems such as drop bottles, plastic bottle nebuliser, automised pump and metered dose pressurised aerosol also showed significant differences in drug distribution in human nose[28,29]. To cite an example, the relative bioavailability and biological response of desmopressin was better with nasal spray than with nasal drops[30].

However, while selecting the excipients and additives for nasal formulations their toxic effects on mucociliary function and nasal epithelium on long term usage should be considered in view of the studies reported by Lee *et al*[31].

DESIGN OF NASAL DRUG DELIVERY SYSTEMS :

The two key factors in the design of an ideal nasal drug delivery system are (a) selection of a suitable absorption enhancer and (b) development

of a dosage form with longer residence time at the site of absorption.

(a) ABSORPTION ENHANCERS : Though the nasal absorption of small nonpeptide drugs is considerable, the nasal bioavailability of peptide and protein drugs is low. The low nasal absorption can be a result of either the poor membrane permeability due to molecular size and/or lack of lipophilicity or the metabolic degradation by aminopeptidases present in the nasal mucosa. To overcome these problems, penetration enhancers have been used to facilitate the transport of protein and peptide drugs and improve their bioavailability.

In general, enhancers improve the absorption of these molecules by one or several mechanisms: 1. Increase the membrane fluidity and reduce the viscosity of the mucus layer 2. Inhibit proteolytic enzymes at the absorption site 3. Transient loosening of the tight junction between certain epithelial tissues 4. Increase paracellular or transcellular transport 5. Dissociate protein aggregation 6. Initiate membrane pore formation 7. Increase nasal blood flow, thereby maintaining the concentration gradient across the nasal mucosa.

Various classes of absorption enhancers together with examples are presented in **Table 1**. It is necessary to ascertain the toxic properties, especially the potential to cause nasal irritation, before absorption enhancers are recommended for inclusion in nasal drug delivery systems.

(b) 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. But for systemic activity, a satisfactory pharmacokinetic profile and good bioavailability are to be provided. Since solution dosage forms are easily subjected to mucociliary clearance, other dosage forms such as suspensions, powders and inserts are developed to improve nasal drug absorption into the systemic circulation. The nasal absorption of human sodium insulin was found to be better from suspensions when compared to solution dosage forms[41]. This might be due to higher drug concentration on nasal membrane which inturn results in an increased concentration gradient for drug diffusion.

Table - I Types of absorption enhancers used in nasal drug delivery systems

Type	Examples
Bile salts[19,32]	Sodium glycocholate Sodium deoxycholate Sodium cholate
Chelators[33,34]	EDTA, Salicylates
Surfactants[19]	Polyoxyethylene lauryl ether Polyoxyethylene sorbitan monooleate
Fatty acids[35]	Sodium caprylate Sodium caprate Sodium laurate
Glycosides[19]	Saponin
Fusidic acid derivatives[31,36]	Sodium taurodihydrofusidate Sodium dihydrofusidate
Phospholipids[37]	Lysophosphatidylcholine Stearoyl lysophosphatidylcholine Palmitoyl lysophosphatidylcholine
Glycyrrhetinic acid derivatives[38]	Sodium glycyrrhetinate Dipotassium glycyrrhizinate Disodium salt of carbenoxolone
Cyclodextrins[39,40]	Dimethyl β-cyclodextrin α-,β-,γ-cyclodextrins

The design of **powder dosage forms** for nasal delivery involves two steps. In the first step, drug is mixed with either a water soluble or a water-dispersible or a water insoluble polymer. In the second step, the mixed powder is dissolved and lyophilised and filled in hard gelatin capsules. By means of a suitable delivery device such as insufflator the contents of the capsule may be administered into the nasal cavity. The efficacy of these systems was dem-

onstrated by the increased nasal absorption of insulin in dogs[42].

Rapid mucociliary clearance of drugs from absorption sites in the nasal cavity is responsible for low bioavailability. In case of peptide and protein drugs the availability is still less because of their physicochemical properties. Hence **bioadhesive systems** are designed where the drug is in contact with nasal membrane for a prolonged period for efficient absorption. These systems utilised **bioadhesive gels** or **microspheres** where the drug is cleared slowly from the mucosal surface.

When bioadhesive excipients such as crystalline cellulose, hydroxypropyl cellulose and neutralised carbopol 934p are mixed with powder dosage forms of insulin, it was found that its nasal absorption was enhanced in dogs[41]. The bioadhesive powder obtained by mixing the freeze dried product of a viscous solution of insulin, polyacrylic acid and hydroxypropyl cellulose with crystalline methyl cellulose led to hypoglycaemic activity equivalent to a third of that obtained by intravenous injection of the same insulin dose[43]. It was concluded that enhanced nasal bioavailability was due to better dispersion of the drug as well as gel formation with methyl cellulose. The nasal absorption of insulin and calcitonin were found increased in rats in 0.1 or 1% polyacrylic acid gel bioadhesive system[44].

Several **bioadhesive microsphere systems** are studied for the administration of insulin[45], hGH[46], oxytocin[47], and propranolol[48]. These systems control the rate of drug clearance from the nasal cavity as well as protect the drug from enzymatic degradation at the site of absorption. Three kinds of microsphere systems are widely studied[49]: 1. Serum albumin microspheres 2. Degradable starch microspheres and 3. Microspheres of DEAE-dextran. **Serum albumin microspheres** are prepared by emulsification of rabbit serum albumin solution in petroleum ether and olive oil and are stabilised by the addition of glutaraldehyde. After separation and washing they are freeze- dried. The diameter of these microspheres ranged from 40 to 60 μm[49]. **Degradable starch microspheres** are prepared by crosslinking starch with epichlorhydrin[50] and their mean diameter is 48 μm. **DEAE-dextran microspheres** are prepared by crosslinking DEAE-dextran with epichlorhydrin and their diameter is 40 to 150 μm.

When all the three types of bioadhesive microsphere systems are evaluated using sodium cromoglycate as a model drug DEAE-dextran microspheres showed less nasal clearance followed by degradable starch and albumin microspheres[49].

ANIMAL MODELS FOR STUDYING THE NASAL ABSORPTION OF DRUGS:

Several *in vivo* and *ex vivo* models have been investigated for studying the nasal absorption of a variety of drugs. One of the widely used models is the rat model which was first reported by Hirai *et al*[51] and later demonstrated by Hussian *et al*[52]. Although several investigators have verified[3,53] the validity of this model or the modified one, it requires the use of surgery and the sealing of the nasopalatine tract with an adhesive agent[3,53]. Recently Lau-Cam *et al*[54] developed a simplified rat model for studying nasal absorption of drugs. In this, the drug solution is to be deposited gradually into the nasal cavity of an anesthetised rat through PE-20 polyethylene catheter connected to a tuberculin syringe via a 30 gauge needle. This model is considered less stressful and more physiological for delivering drugs through nasal route.

Rabbit is another widely used animal model for studying nasal absorption of drugs[3,55]. The other less widely used models[3] include the dog, the sheep and the monkey. For pharmacokinetic and formulation studies, the rabbit, the dog and the sheep models are excellent. An *ex vivo* nasal perfusion model has been described[3] for studying the nasal absorption of drugs. However, the constraints of an animal model still play an important role in the assessment of the nasal delivery of drugs.

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEMS:

1. Drug degradation that is observed in the gastro-intestinal tract is absent.
2. Hepatic first-pass metabolism is absent.
3. Rapid drug absorption and quick onset of action can be achieved.
4. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
5. The nasal bioavailability for smaller drug molecules is good.
6. Drugs that are orally absorbed can be delivered to the systemic circulation by nasal route also.
7. Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
8. Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

LIMITATIONS:

1. The histological toxicity of absorption enhancers used in nasal drug delivery systems is not yet clearly established.
2. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3. Nasal cavity provides smaller absorption surface area when compared to GIT.

CONCLUSIONS:

The systemic administration of potent and labile drugs, especially protein and peptide drugs, is possible by nasal route because of high vascularisation, absence of first pass effect and low aminopeptidase activity. The design of nasal drug delivery systems should involve methods to decrease the nasal clearance and to eliminate any possibility of hydrolysis. This can be achieved by bioadhesive microsphere systems containing absorption enhancers. The aim of many research groups is the development of an acceptable nasal formulation for peptides and proteins such as insulin, calcitonin, human growth hormone, oxytocin, desmopressin and *tetanus toxoid.* However, the clinical efficacy and safety of the nasal drug delivery systems have yet to be clearly established. It is possible that suitable formulations for systemic drug delivery via the nasal route will become available in the near future.

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