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# RECENT TECHNIQUES IN NASAL DRUG DELIVERY: A REVIEW

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## ABSTRACT

*Nasal drug administration has been used as an alternative route for the systemic availability of drugs restricted to intravenous administration. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. The nasal administration of drugs, including numerous compound, peptide and protein drugs, for systemic medication has been widely investigated in recent years. Drugs are cleared rapidly from the nasal cavity after intranasal administration, resulting in rapid systemic drug absorption. Approaches are discussed here for increasing the residence time of drug formulations in the nasal cavity, resulting in improved nasal drug absorption. The article highlights the importance and advantages of the nasal drug delivery systems stressed upon bioadhesive properties. Bioadhesive, or more appropriately, mucoadhesive systems have been prepared for both oral and peroral administration in the past.*

*The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. In this review we discuss the effects of microspheres and other bioadhesive drug delivery systems on nasal drug absorption. Drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics which swell easily when in contact with the nasal mucosa. These drug delivery systems have the ability to control the rate of drug clearance from the nasal cavity as well as protect the drug from enzymatic degradation in nasal secretions.*

***Key words:*** *Drug delivery systems, Gels, Liposomes, Microspheres, Nasal drug absorption*

## Introduction

Nasal delivery is considered to be a promising technique for the following reasons:

- the nose has a large surface area available for drug absorption due to the coverage of the epithelial surface by numerous microvilli,
- the sub epithelial layer is highly vascularized, the venous blood from the nose passes directly into the systemic circulation and therefore avoids the loss of drug by first pass metabolism in the liver,
- it offers lower doses, more rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity fewer side effects, high total blood flow per cm3,

porous endothelial membrane is easily accessible, and drug is delivered directly to the brain along the olfactory nerves[1–3].

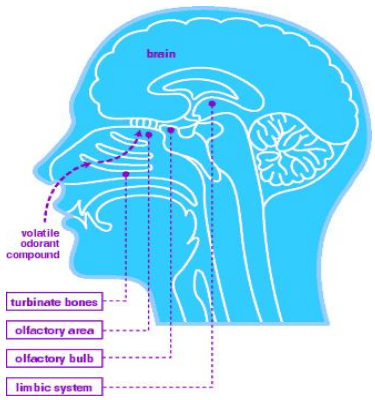


**Figure 1: Nasal Route**

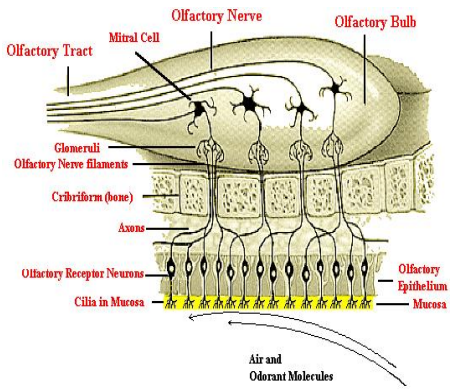


**Figure 2 Detailed Structure of Nasal Mucosa**

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However the primary function of the nose is olfaction, it heats and humidifies inspired air and also filters airborne particulates[4]. Consequently, the nose functions as a protective system against foreign material[5]. There are three distinct functional zones in the nasal cavity, namely: vestibular, olfactory, and respiratory areas. The vestibular area serves as a baffle system; it functions as a filter of airborne particles[6]. The olfactory epithelium is capable of metabolizing drugs. The respiratory mucosa is the region where drug absorption is optimal[7].

To optimize nasal administration, bioadhesive hydrogels, bioadhesive microspheres (dextran, albumin and degradable starch) and liposomes have been studied.

**Factors affecting nasal drug absorption**

The physicochemical properties of the drug, nasal mucociliary clearance and nasal absorption enhancers are the main factors that affect drug absorption through the nasal mucosa. One of the greatest limitations of nasal drug delivery is inadequate nasal drug absorption.

Several promising drug candidates cannot be exploited via the nasal route because they are not absorbed well enough to produce therapeutic effects. This has led researchers to search for ways to improve drug absorption through the nasal route.

***Physicochemical properties of the drug***

The rate and extent of drug absorption may depend upon many physicochemical factors including the partition coefficient of the drug, the pKa, the molecular weight of the drug, perfusion rate and perfusate volume, and solution pH and drug concentration[8]. It has been concluded that *in vivo* nasal absorption of compounds of molecular weight of less than 300, are not significantly influenced by the physicochemical properties of the drug[9]. There is a direct correlation between the log of the proportion of the dose nasally absorbed and the log of the molecular weight[10].

***Mucociliary clearance***

Particles entrapped in the mucus layer are transported with it thus, effectively cleared from the nasal cavity. The combined action of mucus layer and cilia is called *mucociliary clearance*. This is an important, nonspecific physiological defence mechanism of the respiratory tract to protect the body against noxious inhaled materials[11]. The normal mucociliary transit time in humans has been reported to be 12 to 15 minutes[12]. The factors that affect mucocilliary clearance include physiological factors (age, sex, posture, sleep[13], exercise[14]); common environmental pollutants (sulphur dioxide and sulphuric acid, nitrogen dioxide, ozone, hairspray and tobacco smoke[15]); diseases (immotile cilia syndrome, primary ciliary dyskinesia-Kartagener's syndrome, asthma, bronchiectasis, chronic bronchitis, cystic fibrosis, acute respiratory tract infection[15]) and drugs[16] and additives[17].

**Nasal absorption enhancers**

The absorption enhancement mechanisms can be grouped into two classes:

*Physicochemical effects:* Some enhancers can alter the physicochemical properties of a drug in the formulation. This can happen by altering the drug solubility, drug partition coefficient, or by weak ionic interactions with the drug.

*Membrane effects:* Many enhancers show their effects by affecting the nasal mucosa surface[18].

***Strategies for nasal drug delivery:***

*A) Microspheres:* Microsperes of different materials have been evaluated *in vivo* as nasal drug delivery systems. Microspheres of albumin, starch and Diethylamonoethyl (DEAE)-dextran absorb water and form a gel-like layer, which cleares slowly from the nasal cavity.

1) Dextran microspheres were proven bioadhesive microspheres for prolonging the residence time in the nasal cavity. The slowest clearance was detected for DEAE-dextran, where 60% of the delivered dose

was still present at the deposition site after 3 hoirs[19]. However, these microspheres were not successful in promoting insulin absorption in rats[20]. The insulin was too strongly bound to the DEAE groups to be released by a solution with an ionic strength corresponding to physiological conditions. Structural changes due to the lyophilization process were observed in spheres with insulin incorporated, which probably further decreased the release rate[21].

2) Degradable starch microspheres (DSM) DSM is the most frequently used microsphere system for nasal drug delivery and has been shown to improve the absorption of insulin[22], gentamicin[23], human growth hormone[24], metoclopramide[21] and desmopressin[25]. Insulin administered in DSM to rats resulted in a rapid dose-dependent decrease in blood glucose[26,27]. DSM as a delivery system for insulin (2 $IU.kg^{-1}$) has also been tested in sheep. The absolute bioavailability was 4.5% and the time to reach maximum effect, i.e., a 50% decrease in plasma glucose, was 60 min[28].

Studies in rabbits have demonstrated that DSM does not induce serious hystopathological changes to the nasal mucosa. Moreover, the DSM was well tolerated by 15 healthy volunteers and did not cause significant changes in mucociliary transport[29].

The effect of starch microspheres on the absorption enhancing efficiency of various enhancer systems with insulin after application in the nasal cavity of the sheep was investigated. The DSM was shown to synergistically increase the effect of the absorption enhancers on the transport of the insulin across the nasal membrane[30].

*B) Liposomes:* Liposomes have been delivered by various routes. The potential adjuvant effect of liposomes on tetanus toxoid, when delivered via the nasal, oral and i.m. routes compared to delivery in simple solution in relation to the development of a non parenteral immunization procedure, which stimulates a strong systemic immunity. They found that tetanus toxoid entrapped in Distearoylphospatidylcholine (DSPC) liposomes is stable and is taken up intact in the gut[31].

The permeability of liposome entrapping insulin through the nasal mucosa of rabbit has been studied and compared with the permeability of insulin solution with or without pre-treatment by sodium glycocholate (GC). A comparison of the insulin solution and liposome suspension showed that the liposome had permeated more effectively after pre-treatment by GC[32].

The relationship between the rigidity of the liposomal membrane and the absorption of insulin after nasal administration of liposomes modified with an enhancer containing insulin was investigated in rabbits. The nasal administration to rabbits showed high fluidity at 37 °C, caused a high serum glucose reduction, and the reduction effect lasted for 8 hours[33].

The loading and leakage characteristics of the desmopressin containing liposomes and the effect of liposomes on the nasal mucosa permeation and were investigated. The increase of permeability antidiuresis of desmopressin through the nasal mucosa occured in the order positively charged liposomes > negatively charged liposomes > solution[34].

The potential of liposomes as an intranasal dosage formulation for topical application of 5, 6-carboxyfluorescein (CF) was investigated in rats. CF was rapidly absorbed into the systemic circulation and no adhesion of CF to the nasal mucosa was observed. Liposomes suppress drug absorption into the systemic circulation and concurrently increase drug retention in the nasal cavity[35].

*C) Gels:* Chitin and chitosan have been suggested for use as vehicles for the sustained release of drugs. Indomethacin and papaverine hydrochloride were used as model drugs in gel formulations. It was

reported that chitin was able to control the release of the above mentioned agents in gel formulation as compared to the powder formulation [36].

Studies showed that cationic polymer chitosan was fairly mucoadhesive in comparison to polycarbophil as a reference substance. They suggested that a strict distinction should be made between mucoadhesive of dry polymers on a wet tissue in air and mucoadhesion of a swollen hydro gel in the presence of a third liquid phase[37]. Nasal absorption of nifedipine from gel preparations, PEG 400, aqueous carbopol gel and carbopol- PEG has been studied in rats. Nasal administration of nifedipine in PEG resulted in rapid absorption and high Cmax; however, the elimination of nifedipine from plasma was very rapid. The plasma concentration of nifedipine after nasal administration in aqueous carbopol gel formulation was very low. The use of PEG 400 in high concentration in humans should be considered carefully because PEG 400 is known to cause nasal irritation in concentrations higher than 10%[38]. The effect of polyacrylic acid gel on the nasal absorption of insulin and calcitonin was investigated in rats. After nasal administration of insulin its absorption from 0.15 w/v polyacrylic acid gel is greater than with 1% w/v gel. There would seem to be an optimum concentration and possibly an optimum viscosity for the polyacrylic acid gel base[39].

The effects of putative bioadhesive polymer gels on slowing nasal mucociliary clearance were investigated using a rat model. The results indicate that all the formulations decreased intranasal mucociliary clearance, thus increasing the residence time of the formulations in the nasal cavity[40].

*D) Cyclodextrins:* Several compounds have been investigated for their nasal absorption enhancement potential using cyclodextrins as the optimisers. The most studied types are:-natural cyclodextrin, and hydoxypropyl cyclodextrin. Only cyclodextrin is a compendia substance and is being considered for a GRAS (generally recognised as safe) status [18].

Merkus et al. reported a study which investigated the effects of a dimethyl-cyclodextrin (DM-CD) powder formulation on intranasal insulin absorption in healthy subjects and patients with insulin-dependent diabetes mellitus (IDDM). Mean absolute bioavailabilities of 3.1% and 5.1% were achieved in healthy subjects and diabetics[41], respectively.

*E) Fusidic acid derivatives:* Sodium tauro-24,25-dihydrofusidate (STDHF) is the most extensively studied among the derivatives of fusidic acid[42]. On the basis of its characteristics, STDHF was considered a good candidate for the transnasal delivery of drugs such as insulin[43], growth hormone[44] and octreotide[45]. Lee et al. determined the radioimmunoactive bioavailability of intranasal salmon calcitonin in 10 healthy human volunteers. The impoved nasal absorption of calcitonin in the presence of STDHF showed a limited transient irritation of the nasal mucosa in some subjects[46]. Hedin et al. studied the intranasal administration of human growth hormone (hGH) in combination with STDHF at 1% concentration in patients with hGH deficiency. They found that in combination with STDHF, the plasma peak of hGH was similar to the endogenous peak[44]. Laursen et al. used a formulation approach in determining the absorption of growth hormone in human subjects using didecanoyl-L-phosphotidylcholine (DDPC) as an enhancer with different concentrations: 0, 4, 8, 16%. They concluded that increasing the relative concentration of DDPC increases the absorption of nasally administered hGH[47]. Drejer et al. studied intranasal administration of insulin with DDPC in healthy human volunteers. They found that intranasal insulin was absorbed in a dosedependent manner with slight or no nasal irritation[48].

*F)Phosphatidylcholines(PC):* Phosphatidylcholines are surface-active amphihilic compounds produced in biological membranes and liposomes. Several reports have appeared in the literature showing that these phospholipids can be used as enhancers for systemic nasal drug delivery[49].

Newman et al. investigated the distribution of a nasal insulin formulation containing DDPC labelled with 99mTc-human serum albumin (99m Tc-HAS) in human volunteers. From the scintigraphic data, the entire dose from the spray was shown to be deposited in the nasal cavity with no deposition in the lungs[50]. The Novo Nordisk study group reported encouraging results following the nasal administration of an insulin/DDPC microemulsion formulation in human volunteers.

The study demonstrated good absorption of insulin whilst pereventing or minimizing nasal irritation[51].

*G) Bile salts and surfactants:* Commonly used bile salts are sodium cholate (C), sodium deoxycholate (DC), sodium glycocholate (GC), sodium taurocholate (TC), sodium taurodeoxycholate (TDC), and sodium glycodeoxycholate (GDC). Several studies indicate that bile salts can be good optimisers in nasal drug products, through there are some reports indicating that bile salts cause nasal irritation when used above a concentration of 0.3%[52].

When a solution formulation containing insulin and 1% sodium glycocholate (SGC) dosed nasally significant decreases in serum glucose concentrations were observed and there was a positive correlation between the peak serum insulin levels and the dose of insulin applied[53].

Hirata et al. investigated the efficacy of a nasal insulin formulation containing 1% SGC in healthy volunteers and diabetic patients. The nasal formulation resulted in rapid increases in serum insulin levels and decreases in blood glucose levels in healthy volunteers and diabetics[54]. Comparative studies of the effects of intranasal and subcutaneous insulin on fasting and post-prandial blood insulin and glucose concentrations in non-obese patients with non-insulin-dependent diabetes mellitus (NIDDM) showed significant differences in results. A nasal solution formulation of insulin and 1% SGC, administered as a spray, resulted in a monophasic increase in serum insulin levels[55]. Salzman et al. investigated the efficacy of 1% laureth-9 in enhancing the nasal absorption of insulin in patients with IDDM and non-diabetic controls. Insulin was shown to be rapidly absorbed via the nasal route lowering plasma glucose levels to 50% of basal values after 45 min in normal subjects compared to 50% in 120 min in diabetics[56]. Paquot et al. investigated the metabolic and hormonal consequences of an intranasal insulin formulation administration containing 0.25% laureth-9 in healthy 140 volunteers. Increase in plasma insulin levels from 5 to 38 $mU.l^{-1}$ at 15 min with decreases in blood glucose concentration from 4.4 to 3.2 $mmol.\ l^{-1}$ at 45 minutes[57].

**Conclusions**

The nasal cavity has a large surface area and a highly vascularized mucosa. Drugs absorbed by the rich network of blood vessels pass directly into the systemic circulation, thereby avoiding first-pass metabolism. Despite the potential of the nasal route, a number of factors limit the intranasal absorption of drug, especially peptide and protein drugs. These are mucus and epithelial barrier, mucociliary clearance and enzymatic activity. Rapid mucociliary clearance of drug formulations that are deposited in the nasal cavity is thought to be an important factor underlying the low bioavailability of drugs administered intranasally. Increasing the residence time of the drug formulation in the nasal cavity, and hence prolonging the period of contact with the nasal mucosa, may improve drug absorption. The

physicochemical properties of the drugs is also an important factor that affects the nasal drug absorption; a number of lipophilic drugs have been shown to be completely or almost completely absorbed from the nasal mucosa. The nasal route of administration will probably have great potential for the future development of peptide preparations and other drugs that otherwise should be administered parenterally.

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