

Review

Nasal Clearance in Health and Disease

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ABSTRACT

This paper reviews the anatomical and physiological factors of importance for nasal drug delivery and discusses in particular the influence of the nasal mucociliary clearance mechanism on the nasal absorption of drugs. The effect of nasal pathological conditions on the mucociliary clearance mechanism and the possible effect of such disease states on nasal drug transport are also discussed. Strategies for the exploitation of bioadhesive drug delivery systems and especially nasal absorption enhancers for the improvement of nasal drug delivery are evaluated to include considerations of the mechanism of action and correlation between the degree of bioadhesion and absorption enhancement and transport of drugs across the nasal membrane. A range of studies involving bioadhesive/absorption enhancer systems are detailed. A selected bioadhesive material, chitosan, which has been shown to have excellent absorption enhancer properties for a variety of drugs is discussed in some detail.

Key words: nasal clearance, bioadhesion, nasal pathology, chitosan, nasal drug absorption

INTRODUCTION

FOR MANY YEARS, the nose has been exploited for administration of drugs for treatment of local diseases such as nasal allergies, perennial rhinitis, viral infections, and inflammations. More and more interest is now being given to the use of the nasal route for application of systemically acting drugs, especially in crisis treatment where a rapid onset of action is beneficial for the patients such as in treatment of acute pain, migraine, erectile dysfunction, Parkinsons disease, nausea, and insomnia.¹

Small lipophilic drugs are rapidly and efficiently absorbed across the nasal membrane directly into the systemic circulation, and for some drugs, such

as propranol and fentanyl, nasal bioavailabilities can reach up to 100%. For small molecular weight polar drugs and especially for larger hydrophilic drugs (such as peptides and proteins), the nasal route of delivery is less efficient, and the bioavailability seldom reaches higher than 10% and 1%, respectively. However, due to problems with degradation of peptides and proteins in the stomach, and gastrointestinal tract and by hepatic first-pass metabolism, these drugs are difficult to deliver by the oral route. So far, none of the novel oral peptide delivery technologies (e.g., from Emisphere and Nobex) have reached the market in any formulation. Also, the literature suggests that the oral absorption by means of these approaches is low, for example, in the order of 5% or less for insulin.^{2,3}

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The nasal route is a good alternative option to oral delivery and much simpler. However, in order to succeed in efficiently delivering such challenging molecules via the nasal route, it is important to understand fully the nasal environment and physiological functions and how these impact on nasal drug absorption. For example, it is often stated that the mucociliary clearance mechanism together with the poor penetration of the nasal membrane play major roles in preventing nasal absorption of drugs that do not easily cross mucosal membranes.²

NASAL CAVITY

The nasal cavity is about 12 cm long, and has a volume of about 15 mL and a total surface area of about 150 cm². The two halves of the nose can each be divided into three regions, namely the nasal vestibule, the olfactory region, and the respiratory region. The respiratory region comprises three large conchae: the superior, the middle, and the inferior. The anterior part of the nasal cavity is covered by squamous epithelium, which gradually changes in the posterior direction into pseudostratified respiratory epithelium. The respiratory epithelium consists of elongated columnar cells, mucus-containing goblet cells, and basal cells. Below the epithelium is the lamina propria, which contains (among other constituents) blood vessels and mucus secretory cells.

Fifteen percent to 20% of the respiratory epithelial cells are covered with mobile cilia. Cilia are 2–4 μm -long fine, hair-like structures that, due to their coordinated movement, are involved in the propulsion of the mucus across the epithelial surface. In addition, the respiratory epithelium is covered by about 300 microvilli per cell. The mucus secreted by the goblet cells and the mucus secretory cells is rich in complex carbohydrates. The mucus layer that covers the respiratory epithelium consists of a sol layer (a low-viscosity periciliary fluid), which surrounds the cilia, and a more viscous gel layer on top of the sol layer and covering the tips of the cilia.

The function of the nose is that of olfaction, mechanical defense against microorganisms and other particulates reaching the lung, and supply and conditioning of air to the lungs. Recently, researchers at Imperial College London have combined biological mechanics and aeronautical engineering to construct transparent three-dimensional (3D) models of the nose.⁵

In this model, they have mapped out the fluid dynamics of the nose, and found that during breathing there is ample time for heat and water exchange to enable equilibrium to near alveolar conditions. This equilibrium can be maintained under extreme conditions (e.g., hot/humid, cold/dry, cold/humid); however, abnormal blood supply or mucus generation may reduce the rate of heat or moisture flux into the respired air and thereby affect the efficacy of the process.

The most interesting function in the context of this paper is the mucociliary clearance mechanism that plays an important part in removing unwanted material, caught by the mucus, from the nasal cavity and thereby also has an impact on the residence of nasal formulations in the nasal cavity.

Mucociliary clearance mechanism

The mucociliary clearance mechanism provides humans with a very efficient defence system protecting the lungs against inhaled microorganisms, particles, and droplets. These materials will deposit on the nasal mucosa after inhalation, stick to the mucous layer, and be carried posteriorly through the nasal cavity and down the esophagus to the stomach.

The transport of the mucus in the nasal cavity is closely related to the beating pattern of the cilia. Cilia beat in a coordinated fashion, but the cilia beat frequency varies with physiological and experimental conditions. In humans, the frequency is normally about 15–20 Hz, equivalent to about 1000 strokes per minute. Each stroke consists of a rapid forward movement of the stretched cilia (with their tips reaching up into the viscous gel layer) and a slower return movement (where the cilia are bent and only move in the sol layer of the mucus). These coordinated strokes result in the forward movement of the mucus layer with a flow rate of 5 mm/min (with a range of 0.5–23.6 mm/min).⁶ The mucociliary flow can be measured in humans by means of gamma scintigraphy⁷ or a saccharine clearance test.⁸

Influence of disease on the mucociliary clearance mechanisms

The nasal cavity is susceptible to various pathological conditions such as allergic diseases (e.g., allergic rhinitis, pollinosis), polyposis, acute

infections, colds, and Katagener's syndrome. The most common symptoms suffered by rhinitis patients are sneezing, rhinorrhea, and nasal blockage due to the swelling of the mucous lining. The common cold is caused by a viral infection of the respiratory tract, and the symptoms are sneezing, coughing, and thin or thick excessive nasal secretion. These and other conditions may have a profound influence on the environment in the nasal cavity, and thereby the performance of nasal delivery systems and possibly the absorption of the drugs.

It is important to consider the possible effects of pathological conditions in the nose on absorption efficiency. It has been shown that mucociliary clearance can be affected by diseases. Hence, by means of gamma scintigraphy, it was shown in an early study that in patients with nasal congestion (blocked nose), no clearance took place, whereas in patients with copious mucus (runny nose) the rapid clearance of an albumin tracer was seen.⁹ In a similar study, the clearance time of a radiolabeled formulation was found to increase when polyps were present in the nasal cavity.¹⁰ Interestingly, it was shown in another study that the clearance time of an interferon solution was unchanged before and after a challenge with virulent strains of human rhinovirus in the nasal cavity, and no relationship was found between amount of nasal secretion produced and clearance time.¹¹ In a recent study, significantly prolonged nasal mucociliary clearance times (MCT) together with more sinonasal symptoms (SNOT-16) were found in HIV-positive patients as compared to HIV-negative controls.¹² Treatment with guaifenesin for 1 week did not change the MCT, whereas the SNOT-16 score was improved. Impairment of nasal mucociliary clearance was also found in children after radiotherapy for childhood head cancer.¹³ Of interest is also a study investigating the effect of aging on the mucociliary clearance mechanism.¹⁴ It was found that subjects older than 40 had a significantly slower cilia beat frequency and longer MCT than their younger counterparts. It was suggested that this could, in part, explain the increased frequency of respiratory infections in the elderly.

NASAL ABSORPTION OF DRUGS

A variety of products for the delivery of drugs into the systemic circulation via the nose is avail-

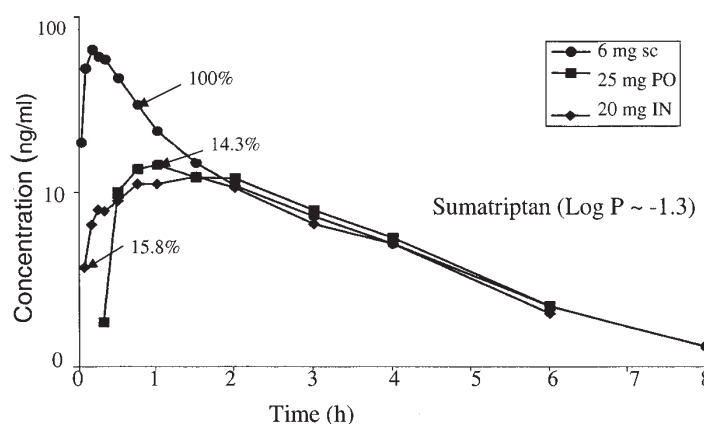
able in the marketplace. Such products include treatments for smoking cessation, hormone replacement therapy, and pain. Nasal products for treatment of Parkinsons disease and erectile dysfunction with apomorphine are in development. Common for these marketed nasal drugs or drugs in development are that they are sufficiently lipophilic to provide adequate nasal absorption. Other marketed nasal drugs comprising peptides and proteins such as calcitonin and desmopressin show a very low nasal bioavailability and would benefit from use of absorption-enhancing delivery systems. A nasal peptide product for treatment of obesity, PYY₃₋₃₆, has been tested in phase 1 and early phase 2 clinical trials.¹⁵ Due to the inherent low nasal bioavailability of the drug, the formulation contains a novel tight junction opener, which increases the transport of the polar drug across the membrane.

As discussed above, the poor uptake of especially polar drugs from the nasal cavity can be associated with three major factors, poor transport across the nasal membrane as well as possible (enzymatic) degradation in the nasal cavity/tissue and rapid clearance from the absorption site. The second factor is of little consequence for most drugs so far studied to date¹⁶ and will not be discussed further here.

Mucociliary clearance is an interesting problem in nasal drug delivery. In man, the clearance of mucus from the nasal cavity by the mucociliary clearance mechanism has a half time of about 15 min. Thus some drugs may not have sufficient time to be fully absorbed before clearance to the gastrointestinal tract occurs. This phenomenon can be exemplified by data on the nasal absorption of two triptan products; nasal sumatriptan (Imigran®) and nasal zolmitriptan (Zolmig®). The total bioavailability in humans for sumatriptan is 15.8%; however, only about 2.5% is due to nasal absorption whereas the remainder (13.3%) is caused by absorption in the gastrointestinal tract after clearance from the nasal cavity (Fig. 1). Zolmitriptan (which is more lipophilic than sumatriptan) shows a higher absorption in man (41%). About 10% is due to nasal absorption and the remainder (about 31% is attributed to oral absorption). Except for an earlier and more rapid initial absorption phase provided by the nasal absorption phase, both of these products show pharmacokinetic plasma profiles very similar to those of the oral products.¹⁷

Formulations that are able to slow down the

FIG. 1. Nasal absorption of sumatriptan as compared to oral and subcutaneous absorption.



clearance process of drugs from the nasal cavity could therefore be advantageous. However, the critical factor for most challenging drugs is one of absorption across the nasal mucosa and as a result, considerable effort has been directed towards the development of technologies that can improve the rate and extent of transport of drugs across the membrane.

Effect of mucociliary clearance and pathological conditions on absorption of drugs

As discussed above pathological conditions and age have been shown to affect the mucociliary transport in human subjects and it is therefore of importance to consider also the possible effect of these conditions on the absorption efficiency of drugs given nasally. It was found early on that an experimentally induced rhinitis had little effect on the luteinising hormone response in human volunteers that were administered busserelin nasally.¹⁸ It was concluded in the study that any modifications to the dosage schedule or delivery route was unnecessary during natural nasal inflammations, such as common cold and allergic rhinitis. Similarly, studies on thyroid stimulating hormone¹⁹ and desmopressin²⁰ both demonstrated no difference in absorption in healthy subjects and in subjects suffering from common colds or rhinitis. In a comparative study between the nasal absorption of triamcinolone acetonide in healthy volunteers and in patients with allergic rhinitis no difference in absorption was seen.²¹ Similar experiments were performed for ipratropium bromide and dihydroergotamine and the results showed no difference in pharmacokinetic parameters between healthy volunteers and volunteers with rhinitis or common colds.^{22,23} It is

reasonable to conclude that although rhinitis and common colds have been shown to have an effect on nasal clearance there has been no indication from the studies performed and discussed above that such diseases would have an effect on the nasal absorption of drugs.

Effect of viscosity and bioadhesion on absorption of drugs

It was shown early on that an increase in the viscosity of a nasal solution formulation with the bioadhesive material hydroxypropylmethyl cellulose (HPMC) resulted in a prolonged clearance rate from the nasal cavity.²⁴ Hence, with progressive increase in concentration of HPMC and thereby also viscosity (0.6%, 0.9%, and 1.25%) progressively increased half-times of nasal clearance times (0.47, 1.7, and 2.2 h) were found in human volunteers. Another study evaluated the effect of gel preparations of roxithromycin prepared with the bioadhesive polymers sodium carboxymethyl cellulose (CMC; 0.7%), hydroxyethyl cellulose (HEC; 0.5%), HPMC (1%), and Carbopol-PEG (1%) on the nasal absorption in rats compared to simple solution formulations of the drug.²⁵ All formulations improved the nasal absorption, the effectiveness being in the decreasing order of CMC > HEC > HPMC > Carbopol-PEG. The same materials were also studied for their effect on decreasing the nasal clearance rate of microspheres administered nasally to rats.²⁶ The effect was most pronounced for MC (3%) > HPMC (3%) > PEG (5%) > CMC (3%) > Carbopol 934 P (0.2%, 0.4%). Recently, it was shown in rabbits that the nasal clearance of formulations with Carbopol 971 P and CMC was faster for the latter.²⁷ In another study it was shown that the

nasal absorption of desmopressin was increased to 27% and 50% when administered in combination with MC and HPMC, respectively as compared to 15% without any bioadhesive material,²⁸ whereas no difference was seen in nasal administration of desmopressin when administered with and without CMC in the formulation.²⁹ From the above studies it can be concluded that a direct relationship between increase in nasal clearance time and drug absorption is not apparent. Furthermore, no direct relationship is apparent between *in vitro* mucoadhesiveness of bioadhesive materials and effect on nasal absorption with CMC, Carbopol 934P, and PEG showing *in vitro* mucoadhesive forces of 193%, 185%, and 96%, respectively.³⁰ Hence, no study has conclusively shown that an increase in viscosity (increase in mucoadhesiveness and thereby decrease in clearance rate) has a significant effect on the absorption of drugs. Therefore, when a bioadhesive material added to a formulation gives an improved absorption of a drug such as for Carbopol 934 P, and HPMC, this is most likely due to an effect of the bioadhesive material on the membrane rather than a "pure" bioadhesive effect (i.e. decrease in nasal clearance time as shown in some papers^{31,32}).

Systems with bioadhesive and absorption enhancing effect

In 1984, it was shown that a bioadhesive powder in the form of crystalline cellulose (CC) mixed with freeze-dried insulin was able to increase the absorption of insulin across the nasal mucosa in the dog.³³ In the same study, the use of Carbopol 934 P or hydroxypropyl cellulose (HPC) prolonged the decrease of plasma glucose but did not decrease the nadir as compared to control. A similar study was performed by another group with octreotide and CC, hydroxyethyl starch, cross-linked dextran, microcrystalline chitosan, pectin and alginate in the rat model.³⁴ The formulations were also characterised in terms of water uptake and calcium binding properties. No correlation was found between degree of water uptake and increase in absorption enhancement whereas the absorption enhancement was directly related to the degree of calcium binding. This result was unexpected since it had been suggested by various researchers, that part of the reason for improvement of the nasal absorption shown by bioadhesive powders was their ability to take up water, form a gel and maintain longer residence time in

the nasal cavity which could possibly be combined with shrinkage of the cells and opening of tight junctions.^{35,36} It was shown by other researchers that the use of powder systems containing no bioadhesive (gelling) material did not improve nasal absorption of the drug in question.^{37,38} As a contrast to these studies the usefulness of bioadhesive formulations for eradication of *Staphylococcus aureus* nasal colonisation was demonstrated by Walsh et al.,³⁹ who administered lysostaphin and an anti-lipoteichoic monoclonal antibody in a bioadhesive cream formulation and in a liquid bioadhesive polymer formulation containing chitosan and polystyrene sulfonate. It was shown that the bioadhesive formulations increased significantly the residence time in the nasal cavity of the rat compared to saline controls, which resulted in significantly reduced CFUs, of 1–6, as compared to a control CFU of 548.

The promising effect of bioadhesive microspheres (administered as a powder formulation) on enhancing the absorption of drugs that did not easily cross the nasal membrane was first demonstrated by Illum et al.⁴⁰ It was shown that gentamicin was absorbed nasally to a negligible degree but when administered nasally with freeze dried starch microspheres to sheep the absorption increased significantly to 10%. With the addition of lysophosphatidylcholine (LPC; a surfactant material), the bioavailability was increased to 57%. Similar enhancements were found for insulin,⁴¹ desmopressin,²⁸ and growth hormone.⁴² A summary of these studies are given in Table 1. It was suggested that the mechanism of action of these bioadhesive microspheres was that of a combination of a longer residence time and an opening of tight junction due to the water absorbing effect of the dry powder.⁴³ Recently, microspheres containing chitosan as the bioadhesive component

TABLE 1. THE EFFECT OF BIOADHESIVE MICROSPHERES ON THE NASAL ABSORPTION OF DRUGS IN SHEEP

Drug	F% <i>rel to SC</i>			
	Control	LPC	DSM	DSM + LPC
Gentamicin	0.6% ^a	0.7% ^a	9.7% ^a	57.3% ^a
Insulin	1.8%	5.9%	10.7%	31.5%
Desmopressin	1.2%	3.2%	4.7%	9.6%
hGH	0.1%	—	2.7%	14.4%

^aF% absolute.

DSM, starch microspheres; LPC, lysophosphatidylcholine; hGH, human growth hormone; F%, relative bioavailability; SC, subcutaneous injection.

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TABLE 2. THE EFFECT OF CHITOSAN FORMULATIONS ON THE NASAL ABSORPTION OF DRUGS IN SHEEP

Drug	F% <i>rel to SC</i>			Molecular weight
	Control	CHI Sol	CHI PWD	
Morphine	10.5%	26.6%	54.6%	~1250 Da
Insulin	0.5%	3.6%	17.0%	~5300 Da
Goserelin	1.5%	11.8%	25.6%	~303 Da

CHI, chitosan; CHI Sol, chitosan solution; CHI PWD, chitosan powder; F%, relative bioavailability; SC, subcutaneous injection.

have been developed for nasal delivery of loratadine.⁴⁴ In these studies chitosan was used either as the only microsphere material or in combination with ethylcellulose and spray dried with the drug. The combination microspheres showed an improved encapsulation efficiency as compared to the chitosan microspheres alone. The microspheres were positively charged and was suggested to have good bioadhesive properties. A range of other bioadhesive microspheres have been used in a similar manner for nasal administration of peptides and proteins and other drugs, such as DEAE-Sephadex,⁴⁵ polyacrylic acid microspheres,⁴⁶ and hyaluronic acid ester microspheres.⁴⁷

Chitosan

In later years a lot of interest has been given to the use of chitosan as a nasal delivery system for systemically acting drugs due to its bioadhesive characteristics and its ability to transiently open the tight junctions. Dramatic improvement in bioavailability has been shown for a range of drugs both in animal models and in humans^{1,4} (Table 2).

Chitosan is a polysaccharide comprising copolymers of glucosamine and *N*-acetyl-glucosamine. It is derived by deacetylation of chitin which is present in crustacean shells. It is available in a range of molecular weights and degrees of deacetylation and as various salt forms. The properties of chitosan, such as pKa and solubility, can be modified by changing the degree of deacetylation and the environment of the formulation, such as pH and ionic strength. The chitosan used pharmaceutically (GMP grade) is produced from the deacetylation of crustacean shells and is a glutamate salt of mean molecular weight of about 250 kDa.

Chitosan can be used nasally both as a liquid and powder formulation. Powders normally pro-

vide an enhanced absorption promoting effect partly due to its increased residence time in the nasal cavity as compared to a liquid chitosan formulation and are especially suitable for drugs that have poor stability in solution such as parathyroid hormone.⁷ As a liquid, a concentration of 0.5–1.0% is very effective. For example, it was shown for the nasal administration a 0.5% chitosan-morphine solution to man that the bioavailability increased from about 10% (for a simple morphine solution) to about 70% (for the chitosan formulation).⁴⁸ Interestingly, the plasma profile obtained resembled the profile obtained after an IV injection with a t_{max} of about 10 min. Similar good results were obtained nasally in sheep for a chitosan based formulation of a LHRH analog, goserelin.⁴⁹ For the peptide PTH, with a nasal bioavailability of about 0.8% when administered as a simple solution, it was possible, by use of various chitosan powder formulations, to increase the nasal bioavailability to up to 25–38% as compared to an IV injection.

Chitosan is not a membrane-active nor surfactant material and as far as can be ascertained in animal models, is not absorbed across mucosal surfaces.¹ Extensive tolerability and toxicological investigations have been conducted which have shown that chitosan is non-toxic when administered nasally and is well accepted by patients.^{8,50} It has been found conclusively in cell models and in animal models that the mechanism of absorption enhancing action for chitosan is that of transiently opening tight junctions combined with a bioadhesive effect in the nasal cavity.^{1,4} It has been shown⁷ that the bioadhesive effect of chitosan is more pronounced for a powder formulation as compared to a solution formulation of

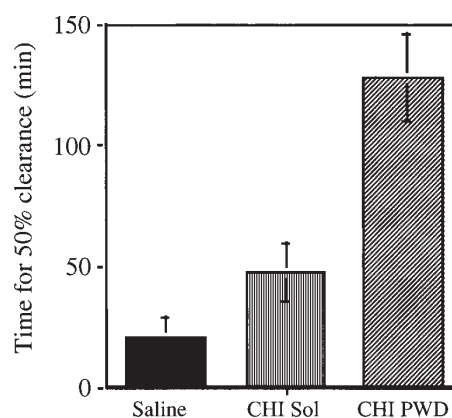


FIG. 2. Nasal clearance of chitosan formulations.

chitosan (Fig. 2). It has also been shown that for some drugs the nasal absorption effect is greater for a chitosan powder formulation as compared to a chitosan solution formulation⁴⁹ (Table 2). Analysis of the cellular fraction of Caco-2 cell monolayers after treatment with chitosan has shown a dose dependent translocation of ZO-1 and occludin from the cytosolic and membrane fractions, where they are available for maintenance of tight junction tightness, into the cytoskeletal fraction.⁵¹ This was caused by a protein kinase C (PKC) activation mechanism.⁵²

CONCLUSION

It can be deduced from the above discussions that, although the nasal mucociliary clearance plays an important part in normal physiological processes in the nasal cavity and that pathological conditions can significantly change the clearance patterns, physiological conditions such as allergic rhinitis and common cold do not seem to have an important effect on the therapeutic efficacy of nasally administered drugs. It has also been shown that the nasal absorption of drugs is not affected significantly. Additionally, it is questionable whether there is a relationship between pure bioadhesion and thereby longer clearance times in the nasal cavity of a material and the ability of this material to increase the nasal absorption of polar drugs that are not easily absorbed across the nasal membrane. However, for absorption enhancer materials with a direct effect on the membrane (e.g., in terms of opening tight junction) that are also bioadhesive, this bioadhesive effect can provide an added positive effect on the absorption enhancement. This has been exemplified by the use of chitosan solutions and chitosan powders, and the increased effect of chitosan powders.

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