



# Nasal Delivery of Proteins and Peptides

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## Abstract

Nasal delivery of protein/peptide drugs has gained considerable amount of attention over the past decade, since it has several advantages over the oral delivery as it avoids harsh gastrointestinal environment, has relatively less enzymatic degradation and relatively highly permeable epithelial mucosa. Nasal products of several small molecular weight (MW < 4000Da) protein/peptide drugs have been approved by the US FDA. This review is focused on the challenges associated with nasal delivery of protein/peptide drugs and possible solutions through various drug delivery technologies.

**Keywords:** Nasal absorption; Intranasal delivery; Proteins; Peptides; Nasal mucosa

## Introduction

Recent years have shown that nasal route can be a potential route for the systemic delivery of protein/peptide drugs as it has a considerably large absorption area (150cm<sup>2</sup>) which is highly vascularized and has permeability similar to or higher than the small intestinal mucosa. Nasal delivery of protein/peptide drugs also offers other benefits such as ease of administration, noninvasive administration, rapid onset of action, and the avoidance of gastrointestinal degradation and hepatic first-pass effects [1]. Nasal route can be utilized to enhance the delivery of drugs to the brain as nose to brain delivery bypasses the blood-brain barrier [2]. However, nasal delivery also suffers from several limitations such as low membrane permeability to hydrophilic molecules (especially when the molecular weight is over several thousand daltons), small applicable volume per dose, enzymatic degradation, and mucociliary clearance [3].

Thus far, several protein/peptide drugs with largest molecular weight being 3432 Da, have been successfully formulated into nasal delivery products and approved by the US FDA. These commercially available drugs include Desmopressin (1183Da), Nafarelin Acetate (1321Da), Oxytocin (1007Da), and Salmon Calcitonin (3432Da) [4]. Nasal delivery of larger molecular weight protein/peptide drugs still remain a challenge, mainly due to the low permeability caused by the drugs being hydrophilic and large in size. Several drug delivery technologies have been explored for these macromolecules but have gained limited success.

## Challenges & Delivery Technologies

Main limitation to nasal delivery of large molecular weight protein/peptide drugs is the low membrane permeability. The rate of permeation is highly sensitive to molecular size for compounds with molecular weight (MW) ≥ 300 Da [5]. A large number of therapeutic agents, peptides and proteins in particular have shown that for compounds >1k Da, bioavailability can be directly predicted from the knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5% [6]. Use of permeation enhancers can help in increasing the transport of proteins and peptides across the nasal membrane [7].

Absorption enhancers such as bile salts, surfactants, fluidic acid derivatives, phosphatidylcholines, cyclodextrins and cell-penetrating peptide (CPP) have been studied to enhance the intranasal absorption of protein/peptide drugs [8]. Absorption enhancers are effective in improving the nasal absorption by either increasing the fluidity of the bilayer of the epithelial cell membrane and thereby opening aqueous pores as a result of calcium ion chelation or by increasing the intracellular delivery using functional moieties [7,9]. Mucolytic agent along with nonionic surfactant has been shown to enhance the nasal absorption of calcitonin in rats and achieved 3.5 times higher bioavailability as compared to the commercial calcitonin nasal spray Miacalcin [10].

Delivery of insulin from nose to the distal regions of the brain was significantly enhanced by L- or D-penetratin as CPP [9]. However, absorption enhancers tend to cause severe nasal irritation and damage the nasal membrane at the concentrations required to effectively promote the nasal absorption [7]. Drug carrier systems such as liposomes, emulsions, nanoemulsions, nano/micro particles and niosomes with permeation-enhancing function, have been evaluated to deliver protein and peptide drugs through nasal cavity. Intranasal delivery of human growth hormone (hGH) - 22kDa protein, using glutathione (permeation enhancer) added microparticles as delivery system increased the relative bioavailability approximately by three folds as compared to the microparticles without glutathione [4]. H102, a novel  $\beta$ -sheet breaker peptide, was encapsulated into liposomes to reduce its degradation and increase its brain penetration through intranasal administration for the treatment of Alzheimer's disease [11].

The study showed 2.92 fold larger AUC in hippocampus with liposomes than a solution of H102 peptide. Mitra et al. [12] reported enhanced absorption of insulin through rat's mucosa using emulsion system. The AUC was observed 4 times higher when insulin was loaded in o/w emulsion as compared to pure buffer solution of insulin. Sintov et al. [13] demonstrated that intranasal delivery of o/w micro emulsion system with 20% water content (insulin in aqueous phase) achieved an absolute bioavailability of 7.5% using rabbit as an animal model. Mucociliary clearance (MCC) is a normal defense mechanism of the nasal cavity that clears mucus as well as substances adhering to the nasal mucosa (bacteria, allergens etc.) and drains them into the nasopharynx for eventual discharge into the gastrointestinal tract. Whenever a substance is nasally administered, it is cleared from the nasal cavity in about 21 min [14]. Thus, MCC reduces the retention time of the drug at the absorption mucosa, resulting in a low bioavailability [3].

Use of mucoadhesive agents has been explored to prolong the intimate contact time of the formulation on the nasal mucosa by adhering to the surface of the mucus layer and thereby enhancing the bioavailability. Nazar et al. [15] studied the effect of insulin loaded hydrogels and observed significant decrease in glucose levels in diabetic rats over the period of 24h. However, it is generally difficult to achieve a satisfactory nasal absorption of macromolecular drugs by increasing the retention time alone because it has to simultaneously overcome the physical barrier of the epithelium for a drug to permeate into the systemic circulation. Also intranasal formulations with mucoadhesive agents have not gained much of a commercial success due to the patient discomfort.

Proteolytic enzymes (amino peptidases and proteases) present in nasal mucosa can be another barrier for intranasal delivery of protein/peptide drugs although the enzymatic activity in nasal cavity is relatively lower than the gastrointestinal tract [16]. Zhou et al. [17] found that the amino peptidase activity in

nasal tissue was about half of that in the intestinal tissue. Enzyme inhibitors have been investigated to protect the protein/peptide drugs from the enzyme activity present in nasal mucosa [18]. Inhibitors with a trypsin-inhibiting activity have been proved to be useful in enhancing the nasal absorption of salmon calcitonin [19].

However, proteolytic enzyme inhibitors themselves cannot facilitate the penetration of drugs across the epithelial membrane and therefore, are generally unable to considerably improve bioavailability in the absence of absorption enhancers. Furthermore, the enzyme inhibitors will affect the normal metabolism of the body, resulting in serious side effects. Therefore, enzyme inhibitors do not seem to be an effective and safe method of improving the nasal absorption of proteins and peptides [20]. Another limitation to nasal delivery is the applicable volume of the formulation which is restricted to 25-250 $\mu$ L per dose. Several approaches have been explored to use this volume effectively which includes the use of solubilizers and gelling agents [21].

### Conclusion

Low molecular weight protein/peptide drugs have been effectively delivered via nasal mucosa. But there is still a need to develop drug delivery systems that can deliver the large molecular weight protein/peptide drugs via nasal route.

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