



## Innovative approaches for nasal drug delivery system and its challenges and opportunities

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### Abstract

Novel drug delivery is one of the fastest growing healthcare sectors, with sales of drugs incorporating novel drug delivery systems increasing an annual rate of 15%, conventionally; the nasal route has been used for the local delivery of drugs for the treatment of nasal allergies and infections. In recent years, research has established that the nasal route is a safe and acceptable alternative to the parenteral administration of drugs. The nasal route has also been found to be useful in targeting drugs to the central nervous system. In addition, absorption of drug at the olfactory region of the nose provides a potential for a pharmaceutical compound to be available to the central nervous system. The nasal delivery of vaccines is another very attractive application in terms of efficacy and patient acceptance. The use of the nasal route for the delivery of challenging drugs has created much interest in recent years in the pharmaceutical industry. A drug molecule can therefore quickly be transferred across the single epithelial cell layer directly to the systemic blood circulation without first-pass hepatic and intestinal metabolism. The effect is often reached within 5 min for smaller drug molecules. Nasal route is a part of drug delivery strategy that is emerging to be a fastest growing drug delivery system with an annual growth of 11% for locally acting drugs & 30% for systemically acting drugs.

**Keywords:** Nasal drug delivery system, Medication, Route of administration

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### Introduction

Nasal administration can therefore be used as an alternative to oral administration of for example tablets and capsules if a fast effect is desired or if the drug is extensively degraded in the gut or liver. Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian medicine. Historically, nasal drug delivery system has received

interest since ancient times Nasal administration can be used to deliver drugs for either local or systemic effect. Locally acting drugs are for example decongestants and allergy treatments. Examples of systemically active drugs available as nasal sprays are migraine drugs, nicotine replacement and hormone treatments. In order to formulate a nasal formulation with desirable performance and commercial attributes, the drug properties, delivery system and nasal physiology should all be considered and understood from the early stages of a product development. It is advisable to focus on maximizing the residence time and ensuring an efficient absorption of drug. A successful nasal formulation program involves detailed consideration of the interactions between formulation composition, device design, delivery system and the patient's pathological condition. If a nasal formulation is delivered to the target site of absorption (turbinates), benefits can be gained from increased absorption and/or decreased dosage requirements. There may also be a reduction of taste of the drug because of minimum or reduced swallowing of the administered drug. Currently, tip aperture design pumps are available to administer formulations in an upward direction. Because the turbinates are located at the sides of the nostrils, the entire dose volume cannot be administered to the target site of absorption. This also leads to swallowing of part of the dose. It may be possible to design a side aperture pump to direct the entire dose volume directly to the absorption site, the turbinates, for more efficient (target) nasal delivery. Nasal sprays for local effect are quite common. Several antimigraine drugs are also currently administered by nasal administration because a fast effect is desired and oral administration can be prohibited by nausea. Peptide drugs (hormone treatments) are also available as nasal sprays, in this case to avoid drug degradation after oral administration. The peptide analogue desmopressin is, for example, available for both nasal and oral administration. The bioavailability of the commercial tablet is 0.1% while that of the nasal spray is 3-5% according to the SPC (summary of product characteristics). Other potential drug candidates for nasal administration include anaesthetics, antiemetics and sedatives that all benefit from a fast onset of effect.

### **Advantages**

- ❖ A noninvasive route and rapid absorption and onset action of drugs.
- ❖ Ease and convenience of administration especially young, the every old and disabled patients
- ❖ Drug degradation that is observed in the gastrointestinal tract is absent.
- ❖ Hepatic first – pass metabolism is absent.
- ❖ Rapid drug absorption and quick onset of action can be achieved.
- ❖ The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
- ❖ The nasal bioavailability for smaller drug molecules is good.
- ❖ Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
- ❖ Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
- ❖ Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

### **Disadvantages**

- ❖ Changes of immunologic reactions.
- ❖ Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.

- ❖ Nasal cavity provides smaller absorption surface area when compared to GIT.
- ❖ Inadequate availability of toxicity data for penetration enhancement.
- ❖ Nasal Pathology may adversely affect the product effectiveness.
- ❖ Rapid mucociliary clearance.

### **Approaches of nasal drug delivery systems**

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. Several approaches are here discussed 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 drug delivery systems applied via the nasal route, which have 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 and that 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. The mechanisms and effectiveness of these drug delivery systems are described in order to guide the development of specific and effective therapies for the future development of peptide preparations and other drugs that otherwise should be administered parenterally. As a consequence, bioavailability and residence time of the drugs that are administered via the nasal route can be increased by bioadhesive drug delivery systems. Although the majority of this work involving the use of microspheres, liposomes and gels is limited to the delivery of macromolecules (e.g., insulin and growth hormone), the general principles involved could be applied to other drug candidates. It must be emphasized that many drugs can be absorbed well if the contact time between formulation and the nasal mucosa is optimized.

### **Strategies for improving drug availability in nasal administration:**

Various strategies used to improve the availability of the drug in the nasal mucosa, include

- 1) To improve the nasal residence time
- 2) To enhance nasal absorption

### **To improve the Nasal residence time:**

Mucociliary clearance acts to remove the foreign bodies and substances from nasal mucosa as quickly as possible. One way of delaying clearance is to apply the drug to the anterior part of the nasal cavity, an effect that is largely determined by the type of dosage form used. The preparation could also be formulated with polymers such as methylcellulose, hydroxy propylmethyl cellulose or polyacrylic acid, in which incorporation of polymer increases viscosity of the formulation and also acts as a bio adhesive with mucus. Increase in residence time does not necessarily lead to increase the absorption; this concept can be illustrated by considering

insulin solution with similar viscosity containing carbopol and CMC. Here carbopol enhance the absorption whereas CMC solution doesn't enhance the absorption of insulin. If we increase the viscosity, slow diffusion of drug from matrix causes retention in absorption with CMC. In case of carbopol causes enhancement of absorption due to opening the intracellular junctions. One more lucrative way to increase the nasal residence time is using biodegradable microspheres as a carrier for drug delivery. Biodegradable microspheres swell in presence of water thereby increasing the viscosity. This phenomenon leads to increase the nasal residence time.

**Enhancing nasal absorption:**

The mechanism of action of absorption enhancer is increasing the rate at which drug passes through the nasal mucosa. Many enhancers act by altering the structure of epithelial cells in some way, but they should accomplish this while causing no damage or permanent change to nasal mucosa.

**Physiochemical Properties of Drugs:****Chemical form:**

The form of a drug can be important in determining absorption. For example, conversion of the drug into an ester form can alter its absorption. It was observed that *in-situ* nasal absorption of carboxylic acid esters of L-Tyrosine is significantly greater than that of L-Tyrosine.

**Polymorphism:**

Polymorphism is known to affect the dissolution rate, solubility of drug and thus their absorption through *biological* membranes. It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders and/or suspensions.

**Molecular Weight:**

A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Daltons. Absorption decreases significantly if the molecular weight is greater than 1000 Daltons except with the use of absorption enhancers.

**Particle Size:**

It has been reported that particle sizes greater than 10  $\mu\text{m}$  are deposited in the nasal cavity. Particles that are 2 to 10  $\mu\text{m}$  can be retained in the lungs, and particles of less than 1  $\mu\text{m}$  are exhaled.

**Solubility and Dissolution Rate:**

Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If drugs remain as particles or are cleared away, no absorption occurs.

**Delivery Systems:**

The selection of delivery system depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences. Some of these delivery systems and their important features are summarized below:

**Nasal Drops:**

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

**Nasal sprays:**

Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200  $\mu\text{m}$ . The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

**Nasal Gels:**

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing device, there was not much interest in this system. The advantages of a nasal gel includes the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target to mucosa for better absorption.

**Nasal Powder:**

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the active drug and /or excipients. Local application of drug is another advantage of this system.

**Conclusion**

Nasal drug delivery offers such benefits as Rapid onset of action with lower dose & minimal side effects. Has an advantage of site-specific delivery with improved therapeutic effects. Attractive for delicate molecules allowing systemic administration without significant degradation. Nasal drug delivery system offers flexibility for multiple formulations ranging from nasal drop to suspension spray recent activities indicate a bright prospect for site-specific delivery of biotechnological products such as Insulin & other hormones. According to a recent report, 13 per cent of the US\$337billion global pharmaceutical market was related to sales of products incorporating a drug delivery system, a figure expected to grow to 20 per cent by 2005. Therefore, although oral delivery remains the preferred option of the patient and the pharmaceutical industry, alternatives such as transdermal, pulmonary and nasal delivery systems are gaining increased interest. Today's nasal delivery technology - the spray pump - has been the status quo for over 25 years. Despite the fact that up to 90% of the drug ends up in the stomach, somehow spray pumps became accepted as nasal drug delivery devices. As the field of biotechnology continues to advance, nasal drug delivery is increasingly becoming a more viable alternative to oral and injectable routes of administration. Recently, it has been shown that many drugs have better bioavailability by nasal route than by oral route.

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