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A Review on Advanced Nasal Drug Delivery System

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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. 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 bio adhesive properties. Bio adhesive, or more appropriately, Mucous adhesive systems have been prepared for both oral and per oral administration in the past. The nasal mucosa presents an ideal site for bio adhesive drug delivery systems.*

Keywords: Nasal, Nasal drug delivery system, route of administration, Nasal Bioavailability

I. INTRODUCTION

Your nose is part of your respiratory system. It allows air to enter your body, then filters debris and warms and moistens the air. Your nose gives you a sense of smell and helps shape your appearance. Many common symptoms affect your nose, such as a stuffy nose and nosebleed. Other symptoms may need treatment to keep your nose functioning well. 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 cm , porous endothelial basement membrane, it is easily accessible, and drug is delivered directly to the brain along the olfactory nerves . However the primary function of the nose is olfaction, it heats and humidifies inspired air and also filters airborne particulates. Consequently, the nose functions as a protective system against foreign material. 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 air bone particles. The olfactory epithelium is capable of metabolizing drugs.

The use of the nasal route for the delivery of challenging drugs such as small polar molecules, vaccines, hormones, peptides, and proteins has created much interest in nowadays. Due to the high permeability, high vasculature, low enzymatic environment of nasal cavity, and avoidance of hepatic first-pass metabolism are well suitable for systemic delivery of drug molecule through nose. Many drug delivery devices for nasal application of liquid, semisolid, and solid formulation are investigated to deliver the drugs to treat most crisis CNS diseases (i.e., Parkinson's disease and

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Alzheimer's disease) because it requires rapid and/or specific targeting of drugs to the brain. It is well suitable for the delivery of biotechnological products such as proteins, peptides, hormones, and DNA plasmids for DNA vaccines to give enhanced bioavailability.

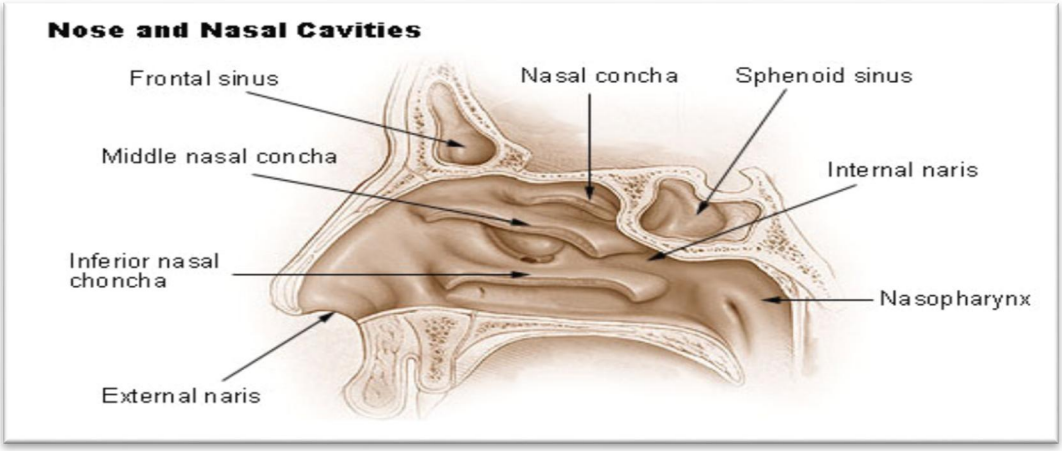

Figure 1: Nose and Nasal Cavities

1.1. Nasal Drug Delivery

Nasal drug delivery is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability. The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible and suitable for self-medication. Currently, two classes of nasally delivered therapeutics are on the market. The first one comprises low molecular weight and hydrophobic drugs for the treatment of the nasal mucosa and sinus, including decongestants, topical steroids, antibiotics and other (OTC) products. The second class encompasses a few drugs, which have sufficient nasal absorption for displaying systemic effects. Important candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, due to their instability in gastrointestinal tract, poor absorption properties, and their rapid and extensive biotransformation Therefore, nasal delivery is promising alternative route for the administration of peptides and protein drugs in particularly.

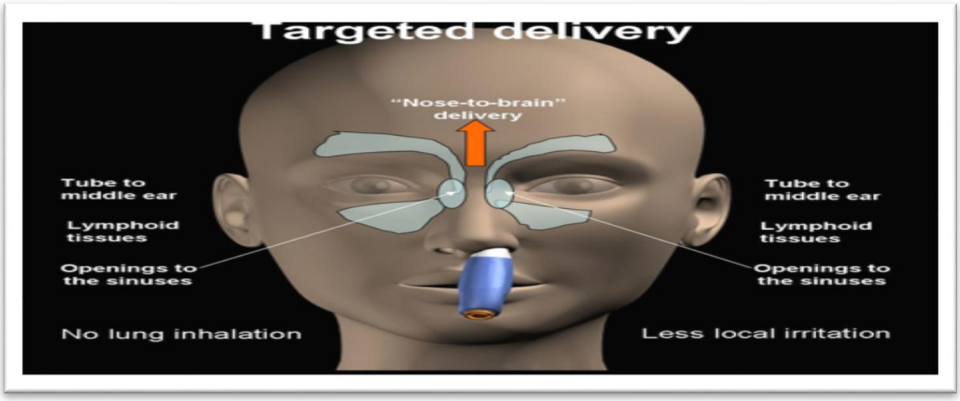

Figure 2: Nasal Targeted Delivery

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1.2. 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. Nasal absorption enhancers involve two main classes. The most important group involve microspheres, liposomes and gels that have been utilized as drug carriers in the past few years.

A. Microspores

Microspores of different materials have been evaluated in vivo as nasal drug delivery systems. Microspheres of albumin, starch and DEAE-dextran absorbed water and formed a gel-like layer, which was cleared slowly from the nasal cavity.

1. Dextran microspheres Illume et al. introduced well-characterized bio adhesive 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 h. However, these microspheres were not successful in promoting insulin absorption in rats20.
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, gentamicin, human growth hormone, metoclopramide and decompressing. Insulin administered in DSM to rats resulted in a rapid dose-dependent decrease in blood glucose. 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.

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 DSPC liposomes is stable and is taken up intact in the gut. 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. 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 h. The loading and leakage characteristics of the decompression-containing liposomes and the effect of liposomes on the nasal mucosa permeation and were investigated. The increase of permeability antidiuretic of decompression through the nasal mucosa occurred in the order positively charged liposomes > negatively charged liposomes > solution. 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.

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

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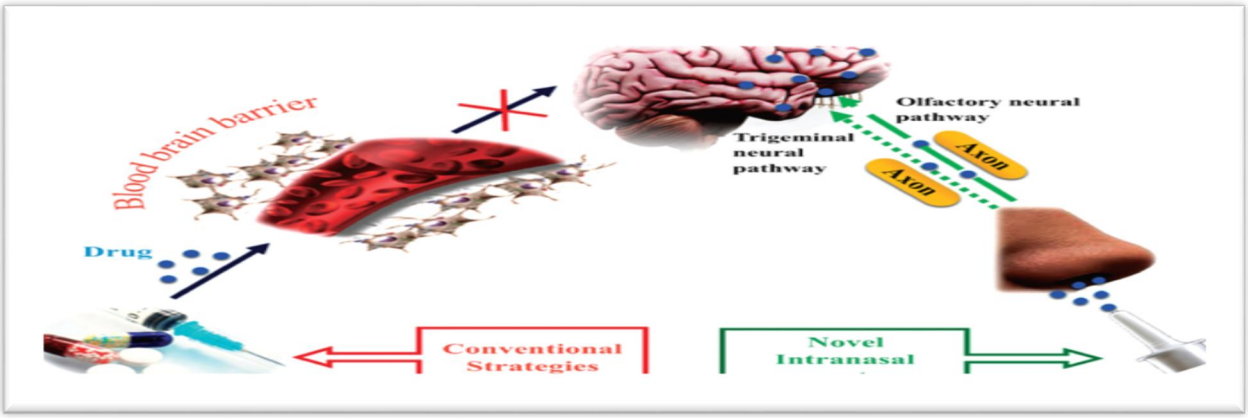
the release of the abovementioned agents in gel formulation as compared to the powder formulation. A similar study done later by Lehr et al. showed that cationic polymer chitosan was fairly mucoadhesive in comparison to polycarbophil as a reference substance. They suggested that a strict distinction 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. 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 C max 138; 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.
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.

II. Mechanism of Nasal Absorption



The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin, it has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.). So many absorption mechanisms were established earlier but only two mechanisms have been predominantly used, such as:

2.1 First Mechanism

It involves an aqueous route of transport, which is also known as the Para cellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.

2.2 Second Mechanism

It involves transport through a lipoidal route and it is also known as the trans cellular process. It is responsible for the transport of lipophilic drugs that show a rate 0dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions.

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III. Development of Nasal Drug Delivery System

- In the development of nasal drug delivery products, Performance targets are met by manipulating the design of the device or the properties of the formulation or both.
- Focusing on nasal sprays, for example, device parameters that can be varied include: the action of the pump and its pre-compression ratio; and the length, geometrynotin orifice size of the actuator. In terms of the formulation, its response to the shear applied by the pump during
- Actuation can be tuned by varying physical properties Such as viscosity, manipulated through the inclusion of modifiers and additives.
- Analytical data support systematic progression towards target bioavailability/ bioequivalence, and later, during manufacture, are also essential for quality control (QC).

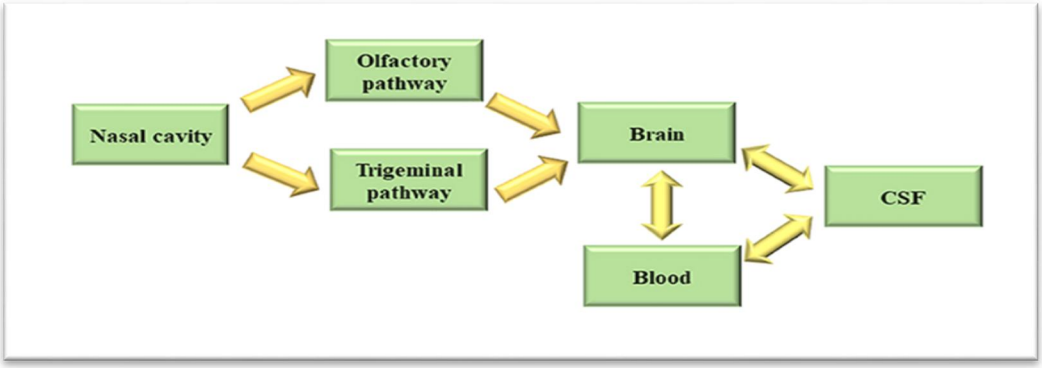

Figure 3: Pathway of Nasal Drug Delivery Activity

IV. Nasal Drug Delivery Devices

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:

4.1 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.

4.2 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 µm. The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

4.3 Nasal Aerosol

In nasal aerosol testing, the guidance notes that the amount of drug deposited below the first stage of the impactor is “of the same order of magnitude as from orally inhaled products” leading to the recommendation that a full APSD is measured. Again, testing is carried out At 28.3 L/min but here smaller expansion chambers tend to be used, with a one liter chamber recommended, since these propellant based devices usually require smaller volumes for the aerosol to become fully developed for QC and bioequivalence applications, testing is always comparative and, it can therefore be argued, the consistency of chamber size/test conditions is the crucial issue.

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4.4 Nasal Gels

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there was not much interest in this system. The advantages of a nasal gel include the reduction of postnasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation using soothing emollient excipients, and target delivery to mucosa for better absorption. Recently, the first nasal gel containing Vitamin B12 for systemic medication has entered the market

4.5 Nasal Powder

This dosage form may be developed if solution and suspension dosage forms cannot be developed 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.

V. CONCLUSION

1. Nasal route is attractive for the delivery of the many drugs and vaccine.
2. Nasal drug delivery system offers flexibility for multiple formulations ranging from nasal drop to nasal spray.
3. Rapid onset of action with lower dose and minimal side effects.
4. It has an advantage of site – specific delivery with improved therapeutic effects.
5. Drug degradation that is observed in the gastrointestinal tract is absent.

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