



REVIEW ON NASAL DRUG DELIVERY SYSTEM WITH RECENT ADVANCEMENT

RAHISUDDIN*, PRAMOD K SHARMA, GARIMA GARG, AND MOHD SALIM

Department of Pharmaceutical technology, Meerut Institute of Engineering and Technology, NH-58, Delhi - Roorkee Bypass Road, Meerut (U.P) - 250005, India. Email: raiselder@yahoo.in

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ABSTRACT

The aim of the present investigation is to explain the recent advancement of nasal drug delivery system. Intranasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. The interest in intranasal delivery of drugs as a non-invasive is increased. We have also discussed advantages, disadvantages, mechanism of action and application of nasal drug delivery system in local delivery, systematic delivery, and Nasal vaccine and CNS delivery of the drug. We are discussed here relevant aspects of biological, physicochemical and pharmaceutical factors of nasal cavity that must be considered during the process of discovery and development of new drugs for nasal delivery as well as in their incorporation into appropriate nasal Pharmaceutical formulations. Nasal route is more suitable for those drugs which cannot be administered orally due to gastric degradation or hepatic first pass metabolism of the drug. Intranasal drug delivery is found much promising route for administration of peptides and protein drugs. Much has been investigated and much more are to be investigated for the recent advancement of nasal drug delivery system.

Keywords: Nasal route, Drug delivery, Gastric degradation, Hepatic first pass metabolism.

INTRODUCTION¹⁻⁸

Intranasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. Nowadays many drugs have better systemic bioavailability through nasal route as compared to oral administration. Biotechnological advancement has led to the development of a large number of protein and peptide drug for the treatment of several of diseases. Oral administration of these drugs is not possible because they are significantly degraded in the gastrointestinal tract or considerably metabolized by first pass effect in the liver. Intranasal drug delivery offers a promising alternative route for administration of such drugs. Nasal drug delivery system is also suitable for restricting and obstacles blood brain barrier so that drug can be delivered in the biophase of CNS. It is also considered for the administration of vaccines. Nasal route has also been considered for the administration of vaccines. The interest in intranasal route for therapeutic purposes arises from the anatomical, physiological and histological characteristics of the nasal cavity, which provides rapid systemic drug absorption and quick onset of action.

Advantages of Nasal Drug Delivery System^{3,9-10}:

1. Drug degradation is absent.
2. Hepatic first - pass metabolism is absent.
3. Rapid drug absorption.
4. Quick onset of action.
5. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
6. Better nasal bioavailability for smaller drug molecules.
7. Drugs which can not be absorbed orally may be delivered to the systemic circulation through nasal drug delivery system.
8. Convenient route when compared with parenteral route for long term therapy.

Limitation¹¹⁻¹²

1. The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.
2. Absorption surface area is less when compared to GIT.
3. Once the drug administered can not be removed.
4. Nasal irritation

MECHANISM OF DRUG ABSORPTION^{3,13-15}

Passage of drug through the mucus is the first step in the absorption from the nasal cavity. Uncharged as well as small particles easily pass through mucus. However, charged as well as large particles may find it more difficult to cross. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.

- The first mechanism of drug absorption involves an aqueous route of transport (Paracellular route). Paracellular route is slow and passive. In above route there is an inverse log-log correlation between the molecular weight of water-soluble compounds and intranasal absorption. Drugs with a molecular weight greater than 1000 Daltons shows poor bioavailability.
- The second mechanism includes transport of drug through a lipoidal route (transcellular process). Transcellular route is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Cell membranes may be crossed by drugs by an active transport route *via* carrier-mediated means or transport through the opening of tight junctions.

Example: Chitosan opens tight junctions between epithelial cells and hence facilitate drug transport.

FACTORS INFLUENCING NASAL DRUG ABSORPTION

The following factors affect drug absorption

1. Nasal physiological factors

Blood flow¹⁶

Rich supply of blood and a large surface area make the nasal mucosa an optimal location for drug absorption. Nasal absorption of drugs is influenced by blood flow rate, as it increases the amount of drug that passes through the membrane and hence reaching the general circulation. Several studies were made to evaluate this influence. For example, Kao et al. stated that nasal absorption of dopamine was relatively slow and incomplete probably due to its own vasoconstrictor effect. From above observations, it was concluded that vasoconstriction decreases nasal drug absorption by diminishing the blood flow.

Mucociliary clearance^{3, 17-20}

Mucociliary clearance (MCC) also referred to as Mucociliary apparatus it is the self-clearing mechanism of the bronchi. Nasal mucus layer defend the respiratory tract by preventing the lungs from foreign substances, pathogens and particles carried by inhaled air. These agents adhere to the mucus layer and transported to the gastrointestinal tract. Above elimination is designated MCC and it influences significantly the nasal drug absorption. The MCC system has been described as a "conveyor belt" wherein cilia provide the driving force whereas mucus acts as a sticky fluid that collects and disposes foreign particles. Hence MCC efficiency depends on the length, density and beat frequency of cilia as well as the amount and viscoelastic properties of mucus. MCC may increased by all factors that increase mucus production, decrease mucus viscosity or increased ciliary beat frequency. In physiological conditions, mucus is transported at a rate of 5 mm/min and its transit time in human nasal cavity is reported to be 15-20 min. The values which are not within the range these references are abnormal and suggestive of impaired MCC. From the above discussion we can say that the residence time of the drugs in nasal mucosa increased and hence permeation may be enhanced when MCC decreases. When MCC increases permeation rate of drug is decreased. MCC does not work properly in the following pathological conditions.

Enzymatic degradation²¹⁻²⁴

Internasally administration of drugs avoids gastrointestinal and hepatic first-pass effect. Drugs may be metabolized in lumen of nasal cavity due to the presence of a broad range of metabolic enzymes in nasal tissues. Some examples of enzyme which may play role in enzymatic degradation of drugs are carboxyl esterase, aldehyde dehydrogenases, epoxide hydrolases, glutathione S-transferases and Cytochrome P450 isoenzymes have been found in nasal epithelial cells. The proteolytic enzymes (amino peptidases and proteases) were also found and they play an important role in degradation of calcitonin, insulin and desmopressin. The pharmacokinetic and pharmacodynamic profile of drugs administered through nasal route may be affected by xenobiotic metabolizing enzymes.

Transporters and efflux systems²⁵⁻²⁷

The absorption of drugs into systemic circulation and CNS through nasal route is of great interest. Multidrug resistance transporters have been identified which may be involved in the transportation of hydrophobic and amphiphilic drugs. The apical area of ciliated epithelial cells and sub mucosal vessels of the human olfactory region contain P-gp is an efflux transporter which plays an important role in avoiding the influx of drugs from nasal membrane.

2. Physicochemical properties of drugs^{24, 28-36}

Some physicochemical properties of drugs (molecular weight, lipophilicity, pKa, stability and solubility) can influence nasal absorption.

Molecular weight, lipophilicity and pKa

Lipophilic drugs such as propranolol, progesterone and fentanyl are well absorbed from the nasal cavity, exhibiting pharmacokinetic profiles similar to those obtained after intravenous administration. These drugs are absorbed quickly and efficiently across the nasal membrane via transcellular mechanisms. This observation is true for lipophilic compounds having molecular weight lower than 1 kDa. The extend of nasal absorption of lipophilic drugs bigger than 1 kDa is significantly reduced. On the other hand, the rate and degree of nasal absorption of polar drugs is low and highly dependent of the molecular weight. Drug absorption is expected to be diminished with decrease lipophilicity because the nasal membrane is lipophilic. Thus we can say that polar drugs may not easily transport across nasal membrane. Whenever lipophilicity is too high, the drug permeation through the wall may be reduced because drug does not dissolve easily in the aqueous environment of nasal cavity.

Stability³⁷⁻⁴⁰

Biological, chemical and physical drug stability studies are a major consideration in all process during the development of new drug formulations. The biological stability of nasally administered drugs may reduce due to the metabolism of drugs by defensive enzymatic mechanisms by nasal cavity. To overcome this difficulty a variety of strategies may be followed, mainly through the use of prodrugs and enzymatic inhibitors.

Solubility^{4, 25, 35, 37}

For drug absorption, drug dissolution is a pre-requisite because molecularly disperse form of a drug may cross the biomembranes. Therefore the drug must be dissolved in the nasal cavity fluid before absorption. Drug allowed enough contact with the nasal mucosa which may show slow absorption. Drugs with poorly soluble in water may require high doses hence can cause a problem. The problem can be overcome by enhancing drug solubility using various techniques.

3. Effect of drug formulation

Viscosity^{35, 41-43}

Formulation with higher viscosity has a better contact time thus increases the absorption. At the same time, high viscosity enhanced the permeability of drugs. This has been observed during nasal delivery of insulin, acyclovir and metoprolol. Zaki et al. observed that the residence time enhanced as viscosity increased but drug absorption diminished.

pH^{18, 25, 37}

The pKa of drug and pH at the absorption site plays important role in absorption of drug through nasal route. Thus the stability can achieve by proper selection of pH of formulation. However, the pH of formulation should be near on human nasal mucosa (5.0-6.5) to prevent the sneezing.

Pharmaceutical form^{3, 4, 44}

Nasal drops are the simplest and the most convenient nasal pharmaceutical dosage form, but the exact amount of drug delivered is not easily quantified and often results in overdose. Moreover,

rapid nasal drainage can occur when using this dosage form. Instead of powder sprays solution and suspension sprays are preferred because powder spray may cause nasal mucosa irritation. Nowadays nasal gel has been developed for accurate drug delivery. This increases the nasal absorption by enhancing the drug residence time and diminishing MCC.

Pharmaceutical excipients^{3,4}

In nasal formulations pharmaceutical excipients are selected accordingly to their functions. The most commonly used excipients are Solubilizers, buffer components, antioxidants, preservatives, humectants, and gelling/viscosifying agents.

APPLICATION OF NASAL DRUG DELIVERY SYSTEM

Local delivery^{3,24}

For the natural treatment of topical nasal disorders the drug is administered through nasal route. Among the most common examples are antihistamines and corticosteroids for rhinosinusitis, and nasal decongestants for cold symptoms. In fact, relatively low doses are effective when administered through nasal route with less systemic toxic effects.

Systemic delivery^{3,41,45-54}

The intranasal administration of drugs is an effective way for systemic availability of drugs as compared to oral and intravascular routes. Actually, it seems to present fast and extended drug absorption, and it has been supported by many studies planned to compare intranasal drug delivery against oral and parenteral administration. Examples include analgesics (morphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir). Some examples which are available in the market include zolmitriptan and sumatriptan for the treatment of migraine and cluster headaches.

Nasal vaccines^{3,25,55-60}

Nasal mucosa is the first site of contact with inhaled antigens and therefore, its use for vaccination, especially against respiratory infections, has been extensively evaluated. In fact, nasal vaccination is a promising alternative to the classic parenteral route, because it is able to enhance the systemic levels of specific immunoglobulin G and nasal secretory immunoglobulin A. Examples of the human efficacy of intranasal vaccines include those against influenza A and B virus, proteosoma-influenza, adenovirus-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus and parainfluenza 3 virus.

CNS delivery through nasal route⁶¹

Intranasal route has promising approaches for delivery of drugs to the brain. The delivery of drugs to the CNS from the nasal route may occur via olfactory neuroepithelium. The transport via trigeminal nerve system from the nasal cavity to CNS has also been described. Drug delivery through nasal route into CNS has been reported for Alzheimer's disease, brain tumors, epilepsy, pain and sleep disorders.

CONCLUSION

The intranasal route is an accessible alternative route for drug administration. This route provides future potential for several

drugs through the development of safe and efficacious formulations for simple, painless and long-term therapy. It is expected that novel nasal products will continue to reach the market due to the widespread benefits of this route. Nasal product will include drugs for acute and long term diseases and also vaccines with better local or systemic protection against infections. From this route drugs can be directly target to the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects. Nasal drug absorption mainly depends on the physiological conditions of the nose and also physicochemical properties of drugs. Much has been investigated and much more are to be investigated for the recent advancement of nasal drug delivery system.

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