INTRANASAL DRUG DELIVERY TO BRAIN: AN OVERVIEW

M. Parvathi
Raghavendra Institute of Pharmaceutical Sciences and Research, Anantapur, Andhra Padesh, India

ABSTRACT
As the people have been suffering from many CNS disorders like Multiple sclerosis, Alzheimer’s disease, Parkinson’s disease many drugs have been developed but they failed in showing the concentration required for action. But nose to brain drug delivery the drug directly enter into the brain. The objective of this review is to provide overview of nose on an physiological, anatomical and, barriers related to nasal drug delivery, physicochemical, biological and factors affecting nasal drug delivery system and its advantages.

Keywords: Intranasal drug delivery, Barriers to intranasal delivery, Brain targeting.

INTRODUCTION
Despite good progress in neurosciences and a corresponding high interest in brain delivery technologies, very few drugs have been marketed for the treatment of CNS disorders. Nasal applications for delivery to the brain have not been pursued by the pharmaceutical industry since the 1980s. Currently, Nasal drug delivery has been recognized as a very promising route for delivery of therapeutic compounds including biopharmaceuticals. The nasal mucosa used for delivering the drugs for CNS disorders and systemic administration of analgesics, sedatives, hormones, cardiovascular drugs, and vaccines, corticosteroid hormones. The anatomy and physiology of the nasal passage indicate that nasal administration has potential practical advantages for the introduction of therapeutic drugs into the systemic circulation. The concentration-time profiles achieved after nasal administration are often similar to those after intravenous administration, resulting in a rapid onset of pharmacological activity. Drugs ranging from small chemicals to large macromolecules including peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity. Marketed products include a range of antimigraine drugs (e.g., sumatriptan, zolmitriptan) as well as some peptides (e.g., calcitonin, desmopressin). Later the use of the nasal route for delivery of vaccines, especially against respiratory infections such as influenza, is attracting interest from vaccine delivery scientists. Bjerre et al. showed that the sedative propiomazine, for which a rapid onset of action is desirable, and it absorbed within 5 minutes after nasal administration to rats. Currently, nasal administration is used therapeutically for the systemic absorption of drugs in a variety of indications, including sumatriptan for migraine, the antidiuretic desmopressin for the treatment of diabetes insipidus and oxytocin for secretion of milk in response to suckling during breast feeding or contraction of the uterine muscle to hasten childbirth by nasal delivery. The dopamine agonist apomorphine for patients with Parkinsonism.

Advantages of intranasal drug delivery
- Rapid drug absorption via highly-vascularized mucosa
- Ease of administration, non-invasive
- Improved bioavailability
- Improved convenience and compliance
- Self-administration
- Large nasal mucosal surface area for dose absorption
- Avoidance of the gastrointestinal tract and first-pass metabolism
- Rapid onset of action
- Lower side effects
Drugs which cannot be absorbed orally may be delivered to the systemic circulation through nasal drug delivery system. Convenient route when compared with parenteral route for long term therapy. Bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

Disadvantages of intranasal drug delivery
- Some drugs may cause irritation to the nasal mucosa
- Nasal congestion due to cold or allergies may interfere with absorption of drug.
- Drug delivery is expected to decrease with increasing molecular weight.
- Frequent use of this route leads to mucosal damage
- The amount of drug reaches to different regions of the brain and spinal cord, varies with each agent

**NASAL CAVITY**

**ANATOMY AND PHYSIOLOGY**

In humans the functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heat and humidify the inhaled air before reaching the lowest airways. Nasal cavity is lined with mucus layer and hairs which are involved in those functions are trapping inhaled particles and pathogens. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures. The nasal cavity is a space situated above the oral cavity and hard palate and below the skull base and intracranial compartment. The nasal septum consists of cartilage in its front end and bone towards the back of the nose. The perpendicular plate of the ethmoid bone, vomer bone, and maxilla bone these three gives nasal septum. The nasal septum is sometimes crooked or off-midline, which leads to narrowing of one or both sides of the nasal cavity. The left and right nasal cavities become continuous in the back of the nose via the opening to the nasopharynx is called as the choana. In this area, the nasal cavity transitions into the nasopharynx. The nasopharynx contains a collection of centrally located lymphoid tissue called the adenoids. The human nasal cavity has a total volume of 15-20 mL and a total surface area of 150 cm². It is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics.

**RESPIRATORY REGION**

The respiratory epithelium is made of with four types of cells are non-ciliated and ciliated columnar cells, basal cells and goblet cells. These cells facilitate active transport processes such as the exchange of water and ions between cells and motility of cilia and also to prevent drying of the mucosa by Trapping moisture in order to facilitate mucociliary clearance. A viscous gel layer, the mucus blanket floats on the serous fluid layer. The viscous gel layer is moved along by the hook shaped cilia termini during the energy dependent ‘effective stroke’ phase of the ciliary motion Cilia are up to 7 mm in length when fully extended but can fold to half this length during the recovery stroke where the hook terminus detaches from the gel layer and moves immersed in the sol layer in the opposite direction to the gel layer movement. The cilia beat with a frequency of 1000 strokes per min. Hence the mucus moves only in one direction from the anterior to the posterior part of the nasal cavity to the nasopharynx.

**OLFACTORY REGION**

Smell allows humans and animals with olfactory receptors to identify food, mates, predators, and provides both sensual pleasure as well as warnings of danger. The olfactory region of the two nasal passages in humans is a area of about 2.5 square centimeters containing in total of about 50 million primary sensory receptor cells. The olfactory region consists of cilia projecting down out of the olfactory epithelium into a layer of mucous which is about 60 microns thick. This mucous layer is a lipid-rich secretion that bathes the surface of the receptors at the epithelium.
surface. The mucous layer is produced by the Bowman’s glands which reside in the olfactory epithelium. The mucus lipids assist in transporting the odorant molecules as only volatile materials that are soluble in the mucus can interact with the olfactory receptors and produce the signals that our brain interprets as odor.

MECHANISM OF DRUG ABSORPTION FROM NOSE

The initial step in the absorption of drug from the nasal cavity is passage through the mucus, large/charged particles may find it more difficult to cross. But Small unchanged particles easily pass through this layer. The mechanisms for absorption through the nasal mucosa. These include paracellular transport via movement between cell and transcytosis by vesicle carriers. transcellular or simple diffusion across the membrane.

1. The first mechanism includes aqueous route of transport, which is also called as the paracellular route. This is slow and passive route. inverse log-log relation ship between intranasal absorption and the molecular weight of water-soluble compounds. Poor bio-availability was observed for drugs with a molecular weight greater than 1000Daltons.

2. The second mechanism is transport through a lipoidal route is known as transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For example, Chitosan, a natural biopolymer opens tight junctions between epithelial cells to facilitate drug transport.

Barriers for nasal drug absorption

Enzymatic barrier

The nasal mucosa contains enzymes such as cytochrome P450-dependent monooxygenase, carboxyl esterase and amino peptidase. nasal delivery avoids hepatic first-pass metabolism to some extent, the enzymes present in nasal mucosa provides a pseudo-first-pass effect. The role of the enzymatic barrier is to protect the lower respiratory airways from toxic agents. In addition, there are various barriers in the nasal membrane for protection from the microorganisms, allergens and irritating substances from the environment that must be overcome by drugs before they can be absorbed into the systemic circulation.

Mucociliary clearance

Particles entrapped in the mucus layer are transported and cleared from the nasal cavity. The combined action of the mucus layer and cilia is called mucociliary clearance. This is a defence mechanism of the respiratory tract to protect against noxious inhaled materials. Mucus traps the particles of dust, bacteria and drug substances and is transported towards the nasopharynx at a speed of 5 - 8 mm/min where it is swallowed. The normal mucociliary transit time in humans has been reported to be 13 to 15 min.

Protective barriers

small molecular weight and Uncharged substances can easily pass through this layer. But larger or charged particles are difficult to cross. Mucin, the protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes such as pH, temperature etc. The nasal membrane is a physical barrier and the mucociliary clearance is a temporal barrier to drug absorption across the nasal epithelium.

FACTORS INFLUENCING NASAL DRUG ABSORPTION

Various factors affecting the systemic bioavailability of drugs that are administered through the nasal route. Those are physiochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system.


2. Delivery Effect Formulation (Concentration, pH) Viscosity Drugs distribution and deposition.

Molecular size
The molecular size of the drug influence absorption of the drug through the nasal route. The lipophilic drugs have direct relationship between the molecular weight and drug permeation whereas water soluble compounds have inverse relationship. The rate of permeation is highly sensitive to molecular size for compounds with MW ≥ 300 Daltons.

Enzymatic degradation in nasal cavity
Nasal cavity having exo-peptidases and endo-peptidases, exo-peptidases capability to cleave peptides at their N and C terminal and endo-peptidases such as serine and cysteine, which can attack internal peptide bonds. Drugs like peptides and proteins are having low bio-availability across the nasal cavity, so these drugs may have possibility to undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier.

Lipophilic-hydrophilic balance
The HLB nature of the drugs affects the absorption process. By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, it appears that these mucosae are primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. Lipophilic drugs like naloxone, buprenorphine, testosterone and 17a-ethynyl-oestradiol are almost completely absorbed when administered intranasal route.

Formulation (pH, Concentration)
The pH of the formulation can affect a drug’s permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria. Concentration gradient plays very important role in the permeation process of drug through the nasal membrane due to nasal mucosal damage.

Viscosity
A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

Drugs distribution and deposition
The drug distribution in the nasal cavity affect the efficiency of nasal absorption. The mode of drug administration could effect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms depends on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation, it enhances the absorption of the drug. The posterior chamber of nasal cavity will use for the deposition of dosage forms depend on delivery device, mode of administration, physicochemical properties of drug molecule.

Environmental pH
The environmental pH also affect the efficiency of nasal drug absorption. The nonionised lipophilic form crosses the nasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous paracellular route.

Membrane permeability
Nasal membrane permeability is the important factor which affects the absorption of the drug through the nasal route. The water soluble drugs and particularly large molecular weight drugs like peptides and proteins are having low membrane permeability are mainly absorbed through the endocytotic transport and by passive diffusion through the aqueous pores (i.e. tight junctions).

Cold, rhinitis
The symptoms are hyper secretion, itching and sneezing mainly caused by the viruses, bacteria or irritants. Rhinitis is a most frequently associated common disease, it influence the bioavailability of the drug. It is caused by chronic or acute inflammation of the mucous membrane of the nose. These conditions affect the absorption of drug through the mucus membrane due the inflammation.

NASAL FORMULATIONS
The selection of delivery system depends upon the drug being used, proposed
indication, patient population and marketing preference.

**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 dose precision. 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 µL.

**Nasal Gels**
Nasal gels are high-viscosity thickened solutions or suspensions. The advantages of a nasal gel include 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 excipients and target delivery to mucosa for better absorption.

**Nasal Powders**
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. Eventhough the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and excipients.

**INTRA NASAL DRUG DELIVERY TO BRAIN**
There are three mechanisms underlying the direct nose to brain drug delivery, one is intracellular transport mediated route and two extracellular transport mediated routes. The intracellular transport mediated route is a relatively slow process, taking hours for intra nasally administered substances to reach the olfactory bulb. The two extracellular transport mediated routes could underlie the rapid entrance of drug into the brain which can occur within minutes of intranasal drug administration. In the first extracellular transport based route intranasally administered substances could first cross the gas between the olfactory neurons in the olfactory epithelium which are subsequently transported in to the olfactory bulb. In the second extracellular transport based route, intranasal administered substances may be transported along trigeminal nerve to by pass BBB. After reaching the olfactory bulb of trigeminal region the substances may enter in to other regions of brain by diffusion, which may also be facilitated by perivascular pump that is driven by arterial pulsation.

Delivery of drugs to the central nervous system (CNS) remains a challenge in the development of therapeutic agents for central targets due to the impenetrable nature of the drug through blood-brain barrier (BBB). The BBB obstruct the substrate penetration based on several characteristics, including lipophility, molecular size and specificity for a variety of ATP-dependent transport systems. Injection of dyes in the ventricles of rabbits and monkeys showed that the cerebrospinal fluid (CSF) is drained via the olfactory neurons into the olfactory neurons, originating from the olfactory bulb, connect the brain with the nasal cavity by penetrating the cribriform plate, which brings the neurons into the nasal mucosa. This coined the idea that this transport route could also exist in the opposite direction, which would imply direct access from the nasal cavity to the brain, thus circumventing the BBB.

**NEEDS AND FUTURE PROSPECTIVE OF NASAL DRUG DELIVERY**
In the field of drug delivery, drug delivery technologies will play a key role in the success of the industry. The need for non-invasive drug delivery systems continues due to poor acceptance and compliance with the existing delivery systems. The current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of poorly absorbed drugs. Key issues facing the biopharma industry are to improve safety, improve efficacy for organ targeting, and improved compliance via sustained release or increasing residence time of drug at the site of application. New technologies include improved nasal formulations; site specific release, carrier-based systems, advanced spray formulations, atomized mist technology, preservative free system and integrated formulation development are strictly needed for success of drug delivery through nasal mucosa.

For success of nasal drug delivery Researchers has to on:
- Development of delivery technologies to increase efficacy and reduce side effects by target delivery with variations potential of the drug
• Development of new technologies to deliver macromolecules with utilization of biotechnology and high technology
• Development of integrated/improved nasal formulations
• Development of integrated device development for successful delivery of therapeutics

CONCLUSION
The identification of ways to increase the bioavailability of drugs in the brain opens possibilities for the causal treatment of diseases associated with a deficiency in neurosteroids and neurotransmitters in the brain. Despite several limitations, intranasal delivery seems to be the most promising application to improve CNS disorders, including Multiple sclerosis, brain injuries, by medicine.

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