ReviewArticle

A Review on Nose-to-Brain Drug Delivery

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ABSTRACT
Intranasal route of administration shows potential for delivery of drugs to brain. The nose-to-brain drug delivery of drugs is advantageous as it requires low dose of drug, avoids first pass effect. Also it is fast in action and suitable for the drugs that degrade in gastrointestinal tract. Nose-to-brain delivery also avoids blood brain barrier which is important factor to be considered in formulation of CNS targeting drugs. This route of administration is also non-invasive, painless and useful in emergency conditions

Keywords: Intranasal drug delivery, Nose-to-brain, olfactory transfer, Drug delivery.

INTRODUCTION

Many drugs are effective at their site of action but in case of central nervous system (CNS) delivery they are discarded during their development for clinical use due to a failure to deliver them in sufficient quantity to the CNS[1]. The presence of a blood-brain barrier (BBB) and a blood-cerebrospinal fluid barrier presents a huge challenge for effective delivery of therapeutics to the CNS. The major problem in drug delivery to brain is the presence of the BBB. Drugs that are effective against diseases in the CNS and reach the brain via the blood compartment must pass the BBB[2]. As a consequence, many diseases of the CNS are undertreated. However, if drug substances can be transferred along the olfactory nerve cells through nose they can bypass the BBB and enter the brain directly (Fig.1). Intranasal administration is a non-invasive method of drug delivery allows therapeutic substances a direct access to CNS.

Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption as it is more permeable than the gastrointestinal tract and has neutral pH. It is also suitable for drugs degrading in presence of gastric enzymes. Intranasal delivery of large molecular weight biologics such as protein, gene vectors, and stem cells is a potentially useful strategy to treat variety of disease of CNS including stroke, Parkinson's disease, multiple sclerosis, Alzheimer's disease, epilepsy, and psychiatric disorders.

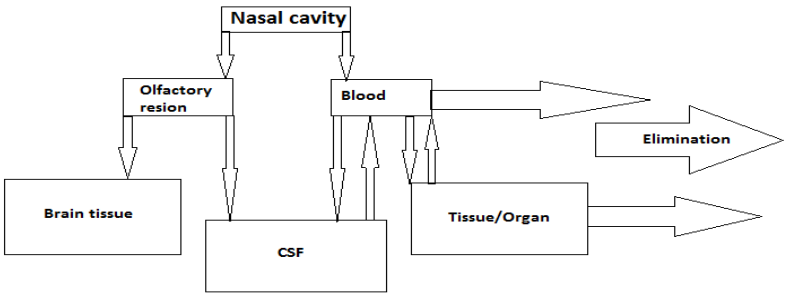


Fig. 1: Nasal Pathway

It is a useful delivery method for drugs that are active in low doses and show no or minimal oral bioavailability such as proteins and peptides.

Merits[3,4]

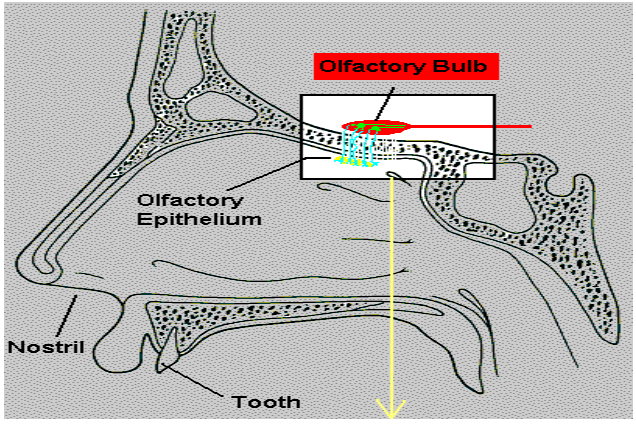
1. Drug degradation that is observed in the gastrointestinal tract is absent.
2. Hepatic first pass metabolism is avoided.
3. Rapid drug absorption and quick onset of action can be achieved.
4. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
5. The nasal bioavailability for smaller drug molecules is good.
6. Drugs that are not absorbed orally can be delivered to the systemic circulation by nasal route
7. Studies carried out so far indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
8. Convenient for the patients, as it is non-invasive and painless, self medication is possible, when compared with parenteral medication.
9. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

Demerits[3,4]

1. The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2. Relatively inconvenient for prolonged use when compared to oral delivery systems since there is a possibility of nasal irritation which may lead to nasal mucosal inflammation.
3. Nasal cavity provides smaller absorption surface area when compared to GIT.
4. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
5. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane if used in high concentration.
6. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

Mechanism of Olfactory transport drug to brain[5]

The major part of the approximately 150 cm^2 surface in the human nasal cavity is covered by respiratory epithelium, across which systemic drug absorption can be achieved. The olfactory epithelium is situated in the upper posterior part and covers approximately 10 cm^2 of the human nasal cavity. The nerve cells of the olfactory epithelium project into the olfactory bulb of the brain, which provides a direct connection between the brain and the external environment (Fig.2).



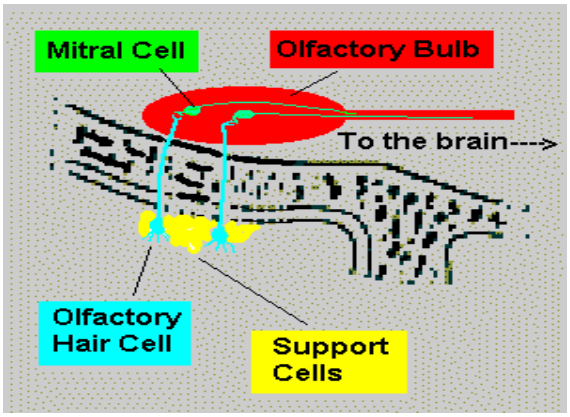


Fig. 2: Olfactory transfer

The olfactory transfer of drugs into the brain is thought to occur by either slow transport inside the olfactory nerve cells to the olfactory bulb or by faster transfer along the perineural space surrounding the olfactory nerve cells into the cerebrospinal fluid surrounding the olfactory bulbs and the brain.

Factors affecting on nose to brain drug delivery[3]

There are several factors that affect the permeation of drugs which are administered through the nasal route. The factors affecting nasal absorption of drug are physicochemical properties of the drug, the effect of nasal environment and characteristics of selected nasal drugs delivery system. These factors play key role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration.

1) Physiochemical properties of drug
- Molecular weight
- Solubility
- Lipophilic-hydrophilic balance.
- pKa

2) Nasal environmental factors
- Blood flow
- Nasal enzymes causing degradation of drug
- Mucociliary clearance(MCC)
- Pathological conditions

3) Formulation factors
- Viscosity
- pH
- Type of dosage form

1) Physiochemical properties of drug

Molecular weight[6]

Polar Drugs having molecular weight below 300 Da show excellent permeation through nasal mucosa because below 300 Da physicochemical properties of drug substance do not significantly affect the rate of permeation through nasal membrane. Lipophilic drugs having molecular weight below 1KDa show excellent absorption through nasal membrane. For polar drugs having molecular weight above 300 Da and lipophilic drugs having molecular weight above 1KDa the rate of permeation reduces significantly.

Solubility[6]

For better drug absorption it is essential that the drugs are water soluble. Before drug absorption through nasal membrane, it should dissolve in the watery fluids of nasal cavity. Due to small size of nasal cavity the availability of fluid for drug dissolution is low hence appropriate aqueous solubility of the drug is essential for better nasal absorption. Poorly water soluble drugs may pose a problem but it can be overcome by using different techniques to enhance aqueous solubility of drug.

Lipophilic-hydrophilic balance[3]

The nasal membrane is lipophilic in nature. So lipophilic drugs are generally well absorbed from nasal cavity presenting nasal bioavailability near to 100%. Polar drugs do not get easily transported across nasal membrane as

composed to lipophilic drugs. But if the drug is highly lipophilic then it does not dissolve in watery fluid present in nasal cavity and absorption is significantly reduced. Therefore a drug should have balanced lipophilicity and hydrophilicity for better nasal absorption.

pKa[3]

According to p^H partition theory the unionized fraction is more permeable than the ionized. It is essential that the drug remains unionized at nasal pH (5.5-6.5) which depends on pKa of drug. Though in ionized form some drugs such as acetylsalicylic acid and benzoic acid have shown absorption to some extent, but unionized species get absorbed four times faster than ionized species.

2) Effect of nasal environment

Blood flow[7]

Nasal mucosa has rich vascularisation and presents large surface area for drug absorption. Blood flow rate determines the rate of drug absorption which takes place by diffusion as the maintenance of concentration gradient across the membrane is essential. So the drugs administered with vasoconstrictors or the drug themselves show vasoconstriction reduce blood flow rate and thus their absorption is significantly reduced.

Drug degrading enzymes[6]

There is a wide variety of enzymes present in the nasal cavity which may degrade the drugs administered intranasally. Enzymes such as carboxyl esterases, aldehyde dehydrogenases, epoxide hydrolases and glutathione S-transferases are present in nasal epithelial cells. Cytochrome P450 isoenzymes are also present which degrade cocaine, nicotine, progesterone and some decongestants. Proteolytic enzymes such as aminopeptidases and proteases are also present and degrade peptide drugs such as insulin and calcitonin. The degradation of drug by nasal enzymes must be taken into consideration for designing nasal drug delivery system.

Mucociliary clearance (MCC)[8]

It is one of the self clearing mechanism of bronchi which plays important role in defense of respiratory tract. The inhaled air contains foreign particles, pathogens which adhere to mucous layer and are transported to nasopharynx and eventually to gastrointestinal tract and prevented to reach lungs. This mucociliary clearance also influences drug absorption. In various pathological conditions Mucociliary clearance is changed, it is either increase or decrease. When mucociliary clearance is decrease drug remains in contact with nasal mucosa for longer time and absorption is increase. When mucociliary clearance is increase drug is rapidly cleared from nasal cavity and absorption is decreased.

Pathological conditions

Common cold, rhinitis and other pathological conditions cause changes in mucociliary clearance affecting nasal absorption of drug. Also hypo secretion and hyper secretion of nasal mucosa influence the drug permeation.

3) Formulation factors[9]

Viscosity

Use of viscosity increasing agent in the formulation increases contact time of drug with nasal mucosa increasing the nasal permeation of drugs. High viscosity formulations also reduce ciliary beating thus reducing MCC.

pH

Buffers are included in nasal drug delivery system to resists change in pH due to nasal secretions. The change in pH of formulation may alter the ionization of drug which may leads to reduction in unionized fraction of drug eventually decreasing absorption of drug through nasal mucosa.

Type of dosage form

Being simple in preparation and easy to use, nasal drops are most commonly used. Solution and suspension type of nasal drops are preferred over powders as powders cause irritation to nasal mucosa. Nasal gels and nasal in-situ gels are preferred over low viscosity nasal drops

as the gels reduce mucociliary clearance, postnasal drip, anterior leakage and localize drug in nasal mucosa to enhance nasal residence Leading to increased permeation of drug.

Different techniques to increase absorption of drugs

Although mucosal membranes are more permeable, nasal mucosa poses some difficulties leading to low nasal bioavailability. There are a number of Factors responsible for this low nasal bioavailability and those factors are rapid enzymatic degradation of drug in nasal cavity, low drug solubility, rapid mucociliary clearance and low membrane permeation. To overcome these problems a number of strategies have been suggested which include use of prodrugs, enzyme inhibitors, and permeation enhancers.

- Prodrug
- Permeation enhancer
- Inhibitors of enzymes responsible for degradation of drugs

Prodrug[10,11]

Prodrug is the inactive molecule, after metabolism forms metabolite which is active. The idea behind this approach is to prepare a pro drug of existing active molecule which has more nasal permeation and less enzymatic degradation. It also aims to have prodrug with better solubility, pKa and stability characteristics as compared to its active molecule.

Example: (1) L-Dopa is poorly soluble in water, so it is very difficult to develop intranasal aqueous formulation with an effective dose. Kao et al. produced various prodrug formulation of L-dopa and he observed that their solubility will increase significantly.

(2) Prodrug of Acyclovir that is L-aspartate-β-ester was more permeable and less labile to enzymatic hydrolysis than Acyclovir.

Permeation Enhancer[6,7]

The permeation of drug can be greatly improved by use of permeation enhancer in the formulation. The enhancers should be non irritant, non toxic, non-allergic and should have reversible immediate effects. Also they should be systemically inert in the concentration used.

The mechanism of action of permeation enhancers is not well known but, they change the permeability of epithelial cell layer by modifying the phospholipidic bilayer, increasing membrane fluidity or opening tight junctions between epithelial cells which increase paracellular transport. The selection of an penetration enhancer depends on its good absorption enhancing property with minimal toxic effects.

Chitosan [12]

Chitosan is a linear polysaccharide biopolymer produced by deacetylation of chitin. Due to its biodegradability, biocompatibility, bioadhesion and nonirritant properties associated to a low toxicity, chitosan is widely used in intranasal formulations. It is believed that it interacts with protein kinase C system and opens the tight junctions between epithelial cells, increasing paracellular transport of polar drugs. It interacts strongly with nasal mucus layer enhancing the contact time for the transport of the drug across the membrane and also enhances the dissolution rate of low water soluble drugs. It used in several intranasal pharmaceutical forms, including powders, liquids, gels, microparticles and microspheres.

Cyclodextrins[13,14]

Cyclodextrins are cyclic oligossacharides composed of glucose units joined trough α-1, 4-glycosidic bonds resulted from bacterial digestion of cellulose. Structurally, they have a hydrophilic outer surface and a lipophilic central cavity in which polar drugs can be included. Cyclodextrins work as absorption enhancers interact with the lipophilic components of biological membranes changing their permeability.

Surfactants[9]

Surfactants such as bile salts are mostly used and several other promoters are also investigated subsequently. Non-ionic and anaionic surfactants including bile salts

were found to enhance the nasal absorption of the drugs by multiple mechanisms such as alteration of the mucous layer, opening of the tight junctions between the epithelial cells, reversed micelle formation in the membrane, extraction of membrane components by co-micellisation and inhibitory effects on proteolytic enzymes.

Inhibitors of enzymes responsible for degradation of drugs

Metabolism of drug in nasal cavity due to presence of enzymes significantly affects nasal bioavailability of drugs. It is necessary to include inhibitors of these enzymes during formulation.

Example: Bestatine and comostate amylase are used as aminoptidases inhibitors and leupeptine and aprotinin as trypsine inhibitors involved in the degradation of calcitonin. Bacitracin, amastatin, boroleucin and puromycin have been used to avoid enzymatic degradation of drugs such as leucine , enkephalin and human growth hormone.

Novel intranasal drug delivery systems to target CNS

Over last few years novel drug delivery systems such as liposomes, micro and nanoemulsions, microspheres, micro and nanoparticles have been used to improve nasal drug permeation.

Liposomes[15]

Liposomes are non-toxic, biodegradable and biocompatible lipid carrier made up of animal lipid such as phospholipids and sphingolipid. They having advantage of carrying hydrophilic, lipophilic and amphoteric drug molecules entrapped inside or on its micellar surface. Mostly lipids are used in liposomal drug delivery are phospholipids which forms self sustained bilayer structure to form liposomes of various size such as small unilamellar vesicles to multilamellar vesicles. Brain distribution of long circulating liposomes can be used to directly encapsulate drug molecule to diseased tissues or organs. The basic mechanism by which liposomes achieve brain concentration by crossing brain brain barrier is by coupling with brain drug transporter vector through absorptive mediated transcytosis.

Nanoparticles[15-16]

Nanoparticles are colloidal systems with compact structure where the therapeutic agent is either entrapped within colloidal matrix or coated on the particle surface by conjugation or adsorption. Nanoparticles can provides sustained and controlled drug release, they are mostly made up of polymer, lipid or combination of both. Nanosystems employed for the development of nano drug delivery systems in the treatment of CNS disorders include polymeric nanoparticles, nanospheres, nanosuspensions, nanoemulsions, nanogels, nano-micelles and nano-liposomes, carbon nanotubes, nanofibers and nanorobots, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and lipid drug conjugates (LDC).

The correct mechanism of barrier opening by nanoparticles is not exactly known. But the delivered nanoparticles enter into the brain by crossing the BBB by various endocytotic mechanisms. The polymeric nanoparticles made from albumin or poly(butylcyanoacrylate) are reported to enter into the brain by their small size mediated endocytosis. These nanoparticles travel intact and release the drug in brain microenvironment directly which is finally biodegraded due to endocytotic uptake because of very small size by BBB.

Microsphere[16]

Microsphere technology is one of the specialized systems becoming popular for designing nasal products, as it provide prolonged contact with the nasal mucosa and thus enhances absorption and bioavailability. In the presence of microspheres, the nasal mucosa is dehydrated due to moisture uptake by the microspheres. This result in reversible shrinkage of the cells, providing a temporary physical separation of the tight (intercellular) junctions that increases the absorption of the drugs. Microsphere used in nasal drug delivery is water insoluble but absorb water into matrix resulting swelling of the spheres to form a gel. The

materials used in formulation of microspheres are starch, dextran, albumin, and hyaluronic acid. Starch and dextran microspheres administered repeatedly. Bioavailability of protein and peptides has been improved in different animal by microsphere formulation. Some low molecular weight drugs also successfully delivered in microsphere formulation. Microspheres have been reported to be present up to 3-5 h in the nasal cavity depending upon the bio-adhesive material used for formulation. The ideal microsphere particle size requirement for nasal delivery should range from 10 to 50 µm as smaller particles than this will enter the lungs.

Microemulsions[17]

Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a co surfactant. These systems are currently of interest to the pharmaceutical scientist because of their considerable potential to act as drug delivery vehicles by incorporating a wide range of drug molecules. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, and improved drug solubilization and bioavailability. Preparing a pharmaceutically acceptable dosage form demands a clear understanding of the micro-emulsion structure, phase behavior, factors leading to its thermodynamic stability, factors influencing drug release from the formulation, requirements of ideal microemulsion excipients, and the potential uses and limitations of the microemulsion system.

Table 1: Review of research on nose-to-brain drug delivery

Author	Category	Drugs	Drug delivery system	Reference No.
Luppi et al 2011	Anti-Parkinsonism	Tacrine	Nanoparticles	18
Tang et al 2008	Brain damage, Dementia	Ergoloid mesylate	Nasal solution	19
Wang et al 2008	Anti-alzheimer	Estradiol	Nanoparticles	20
Patel et al 2011	Antipsychotics	Risperidone	Nanoparticles	21
Lai et al 2011	Anti-Parkinsonism	Odorranalectin	Nanoparticles	22
Fazil et al 2012	Anti-alzheimer	Rivastigmine	Nanoparticles	23
Desai et al 2010	Anticonvulsant, Anxiolytic	Midazolam	Microspheres	24
Zhang et al 2004	Antihypertensive	Nimodipine	Nasal Solution	25
Eskandari et al 2011	Antiepilepics	Valproic acid	Nanostructured lipid carriers	26
Vyas et al 2006	Hypnotic's , Sedative	Clonazepam	Microemulsion	27
Rasal et al 2010	Anti-Migraine	Sumtriptan	Microemulsion	28
Majithiya et al 2006	Anti-Migraine	Sumtriptan	Thermoreversible-mucoadhesive gel	29
Barakat et al 2005	Antiepileptic	Carbamazepine	Gel	30
Misra et al 2009	Antipsychotics	Olenzapine	Nanoemulsion	31
Sharma et al 2012	Antiepileptic	Gabapentine	Microsphere	32
Bhanushali et al 2009	Anti-migraine	Rizatriptan benzoate	Nanoemulsion	33
Kumar et al 2008	Antipsychotics	Risperidone	Nanoemulsion	34

CONCLUSION

Intranasal drug delivery has been practiced for thousands of years. It is experiences certain advantages of non-invasiveness over parenteral administration and quick onset of action over oral administration. It is also a promising alternative to drugs that remain unabsorbed or degrade in gastrointestinal tract. Intranasal route has shown one very important advantage of delivering drug directly to brain by bypassing blood brain barrier. This route has shown great potential to directly target the brain with reduced systemic side effects. Few CNS drugs are already in market as their intranasal delivery system. However there are number of limitations which should be overcome to develop successful nose-to-brain drug delivery system. A number of novel formulations have been used to target brain via nasal administration. However more efforts are needed to make this route more efficient and popular for brain targeting.

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