



NASAL DRUG DELIVERY: A POTENTIAL ROUTE FOR BRAIN TARGETTING

Siva Reddy P*, Sreekanth Nama, P. Srihari, K. Sasikanth, Prasanna Kumar Desu

Department of Pharmaceutics, Priyadarshini Institute of Pharmaceutical Education & Research (PIPER),
5th Mile, Pulladigunta, Kornepadu (V), Vatticherukuru (M), Guntur-522017, Andhra Pradesh, India.

ABSTRACT

Present review highlights the potential of nasal mucosa as an administration route for targeting the central nervous system, the brain. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of medication in the remaining tissues. Thus improving efficacy of the drug and reducing side effects. The nasal mucosa when compared to other mucous membranes is easily accessible and provides a practical entrance portal for small and large molecules. Intranasal administration offers rapid onset of action, no first-pass effect, no gastrointestinal degradation or lung toxicity and non-invasiveness application and also improves bioavailability. It is thought that olfactory route of drug transport, by pass the blood-brain barrier and allows the direct transport of drug from the nose to the brain. This review provides an overview of strategies to improve the drug delivery to brain via nasal mucosa and recent advances in this field.

Keywords: Nasal Delivery, Brain targeting, Blood-Brain barrier (BBB), Central nervous system (CNS), Cerebrospinal fluid (CSF).

INTRODUCTION

Despite tremendous advances occurring in brain research, brain and central nervous system disorders like schizophrenia, meningitis, migraine, Parkinson's disease and Alzheimer's disease remains the world's leading cause of disability, and account for more hospitalizations cases and prolonged care than accounted for almost all other diseases combined. The major problem in drug delivery to brain is the presence of the BBB. Brain is tightly segregated from the circulating blood by a membranous barrier called the Blood Brain Barrier (BBB). The major challenge in CNS drug delivery is the blood-brain barrier (BBB), which limits the access of most drugs to the brain. Advances in understandings of the cell biology of the BBB have made new avenues and possibilities for improved drug delivery to the CNS. It is well established that the BBB is a membranous barrier that segregates the brain from the circulating blood [1]. The second barrier that a systemically administered drug molecule encounters before entering the CNS is the blood-cerebrospinal fluid barrier (BCB). As the CSF has the ability to exchange molecules

with the interstitial fluid of the brain parenchyma, the passage of blood borne molecules into the CSF are also carefully regulated by the BCB. The BCB is found in the epithelium of the choroids plexus, and is arranged in such a manner that it limits the passage of molecules and cells into the CSF. Nasal route has been explored as the conventional route, for the local delivery of drugs for treatment of local diseases like nasal allergy, nasal infections, rhinitis and nasal congestion. Since last few decades, nasal route had attracted a wide attention for researchers as a convenient, reliable and a safe route to achieve faster and higher levels of drug absorption. Most of the therapeutic agents have been abandoned because sufficient amount of drug levels in the brain have not been achieved by the drugs via the systemic circulation. Macromolecular drugs like peptides and proteins, termed as "biologics" are too large and too hydrophilic to penetrate the BBB from the systemic circulation. The major disadvantage with them is that they would be rapidly degraded by gastrointestinal enzymes or by the liver cytochromes, if taken orally. A non-invasive therapy

seems to be desirable for the patients particularly for diseases that require chronic dosing related to dementia. It has been proved theoretically in the animal and human investigations that transport of exogenous materials directly from nose-to-brain is a potential route for bypassing the BBB [2].

Conventional Brain Targeting Strategies

INVASIVE STRATEGIES:

Disruption of the BBB

The thought behind this approach is the shrinkage of BBB momentarily by injecting mannitol solution into arteries in the neck. The resulting high sugar concentration in brain leads to the following steps

- Capillaries take up water out of the endothelial cells.
- Shrinkage of endothelial cells.
- Thus opening tight junction.

The effect lasts for 20 to 30 minutes, which is sufficient for the drugs to diffuse freely, that would not normally cross the BBB. In addition to opening of junction complexes and formation of inter endothelial gaps, trans-endothelial opening and tracer passage through the cytoplasm of injured endothelial cells were also observed in response to the hypertonic barrier disruption [2,3].

Intracerebral Implants

Intracerebral chemotherapeutic implants are the controlled release systems which increases the survival of human with recurrent malignant gliomas and of animals with transplanted gliomas. Drug added to polymer pellet implants intra cranially bypass the BBB and release drug molecules locally in the brain in a sustained fashion. Malignant gliomas are located deeply in the brain and thus the effectiveness of the drug delivered by the polymer is dependent on whether drug molecule can be transported a sufficient distance from the implanted site to reach malignant gliomas. Intracerebral delivery involves delivery of drug directly into parenchymal space of the brain. Drugs can be injected directly (bolus or infusion) via intrathecal catheters, by controlled release matrices, microencapsulated chemicals¹⁶ or recombinant cells. The major problem with bolus injection is slower movement of compounds within the brain due to the limited diffusion coefficient. The reason behind this is, due to the closely packed arrangement of cells in both gray as well as white matter microenvironment and due to the concentration dependent diffusion phenomena in brain. Hence a large amount of dose is required for an appropriate drug concentration in parenchyma. Alternatively the continuous infusion method can be used which uses convection enhanced diffusion (CED) phenomena to drive the drugs to a larger tissue region [3, 4].

Intraventricular Delivery

Intraventricular route also act as an approach to bypass BBB by neurosurgical means where therapeutic agents are instilled directly into cerebral ventricle. This route is best suited for meningioma treatment and metastatic cells of CSF as it distribute drugs mainly into ventricles and subarachnoidal area of brain. Major advantage of this route is that, its lack of interconnection with interstitial fluid of brain unlike intracerebral delivery. Thus the drug achieves higher concentration in brain in comparison to that of its extra vascular distribution. But the major disadvantages are the chance of causing subependymal astroglial reaction due to high drug exposure at the ependymal surface of brain.

Intrathecal delivery (Intra-CSF drugdelivery)

Intrathecal route involves delivery of neurotherapeutic agents to brain by direct administration of drugs through intrathecal route into cisterna magna of brain. Though it is substantially less invasive than intraventricular administration, but this method fails to result indrug accumulation in parenchymal structures of the deep brain which is highly essential for sustained drug release²⁰. The major disadvantage of this route is the chance of understood when etoposide administered through this route into the dogs led to ataxia and loss of muscle coordination. Due to this, intrathecal route is best suited for drug delivery for treatment of spinal diseases and disseminated meningeal diseases but not for large parenchymal diseases like parenchymal tumors such as glioblastoma [3, 4].

PHYSIOLOGICAL STRATEGIES

Pseudo nutrient Approach

Pseudo nutrient Approach Peptide drug design incorporates a specific molecular characteristic that facilitates the drug to be transported by one or more of the inwardly directed nutrient carriers. The BBB expresses several systems for the transport of nutrients and endogenous compounds. Utilization of these transport systems is a potential strategy for controlling the delivery of drugs into the brain. These drugs must have a molecular structure that mimic the endogenous nutrient. The hexose, large nutrient amino acid carrier have the highest capacity and are best suited for the delivery of substrates to the brain [4].

Ligand Binding Proteins

Protein ligands possesses various properties such as high affinity to receptors and selectivity for targeting, which increases the interest towards the use of proteins as a delivery tool for targeting drugs to the brain. Central ligand binding component such as lectins act as a ligand binding protein for brain targeting of glucose triggered glycosylated insulin and bispecific antibodies. Cationized albumin appears to be useful for the Delivery of the active

agents across the BBB to the brain. Other ligand binding protein classes include biotin-binding proteins, lipid binding proteins and avidin binding proteins. Like avidin biotin conjugates immunoglobulins occupy a special place in the field of ligand binding proteins because of their ability to recognize almost infinite number of ligand molecules [4, 5].

Chimeric Peptides

Synthesized chimeric peptides are another possibility for the drug delivery to the brain. Chimeric peptides are generated by linking of a drug which lacks transport at BBB to a vector at the luminal membrane of brain capillary endothelial cells. The vector initiates receptor-mediated or adsorption-mediated transcytosis.

PHARMACOLOGICAL STRATEGIES

Pro-drug Based Brain Targeting

Brain uptake of drugs can be improved by prodrug formation. Prodrugs are pharmacologically inactive compounds that result from chemical modifications of biologically active species. The chemical change is designed to improve some deficient physicochemical property, like membrane permeability and water solubility. After administration, the prodrug, by virtue of its improved characteristics, is brought closer to the receptor site and is maintained there for longer periods of time. Here it gets converted to the active form. Once in the CNS, hydrolysis of the modifying group will release the active compound and is ready to show therapeutic activity [5, 6].

Nanoparticles

Nanoparticles are solid colloidal carrier particles ranging 1 to 1000 nm in size. They consist of macromolecular materials in which the active principle is dissolved, entrapped or encapsulated or to which the active principle is adsorbed or attached [6].

Enhancement of the drug transport across the BBB by means of nanoparticles:

- Nanoparticles are preferably absorbed on the wall of the brain blood vessels without transport of particles across the endothelium.
- The fluidization of the endothelium by the surface activity of the surfactant polysorbate 80 is known to enhance the drug transport across the brain.
- Opening of the tight junction between the endothelial cells lining the brain.
- Endocytic uptake by the endothelial cells
- Lining of the brain blood vessels with or without degradation of the nanoparticle.
- Transcytosis across the brain endothelial cells. After the uptake of the nanoparticle by the endothelial cells, the nanoparticles and adsorbed drug may be delivered to the

brain cells by transcytosis.

- The inactivation of p-glycoprotein flux pump has been reported to enhance the brain transport of nanoparticle.

Liposomes

Liposomes are the biocompatible, nontoxic, biodegradable lipid vesicles first characterized by Bangham. Liposomes were initially developed as models of biological membranes. Liposomes are well defined lipid vesicles that offer an immense advantage of targeting the drug to selected tissues using appropriate modifications mediated by either passive or active mechanisms.

Liposomes offer the possibility of carrying hydrophobic, hydrophilic or amphoteric molecules. They can act as carrier for drugs, enzymes, proteins, anticancer substances and other macromolecules. Liposome based anticancer chemotherapy offers the advantage of reduced systemic toxicity to other cells and combined with selective drug delivery into tumor [6, 7].

Nanoconjugates

These are low molecular weight conjugates of a small drug or toxin and targeting the ligands, coupled through a cleavable linker group. It consists of three functional domains, the targeting groups, linker and an active drug/agent. The drug transport and distribution in the interstitium depends on convection and diffusion.

NASAL CAVITY ANATOMY, PHYSIOLOGY AND HISTOLOGY

The major functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heats and humidifies the inhaled air before reaching the lower airways. The nasal cavity is lined with a mucus layer and hairs which are involved in functions like trapping inhaled particles and pathogens [6]. Moreover, resonance of produced sounds, mucociliary clearance (MMC), immunological activities and metabolism of endogenous substances are also essential functions of nasal structures. Anatomic and histological characteristics of the different areas of the nasal cavity allow these functions to be performed optimally. Anatomically, the human nasal cavity fills the space between the base of the skull and the roof of the mouth, above it is supported by the ethmoid bones and, laterally, by the ethmoid, maxillary and inferior conchae bones. The total volume of the human nasal cavity is 15-20 mL and the total surface area is approximately 150 cm². It is divided by the middle or nasal septum into two symmetrical halves, each with one opening at the face through the nostrils and extending posteriorly to the nasopharynx [8].

Olfactory Region

The olfactory region is located in the roof of the nasal cavity and extends down the septum and lateral wall. Neuroepithelium is the only part of the CNS that is directly

exposed to the external environment. In the respiratory epithelium, the olfactory one is pseudo stratified but contains specialized olfactory receptor cells important for smell perception⁴⁶. In this area there are some small serous glands (glands of Bowman) which produces secretions acting as a solvent for odorous substances [9].

Advantages of nasal microspheres

- Degradation of drug does not occur.
- Absence of Hepatic first – pass metabolism.
- Rapid drug absorption.
- Quicker onset of action.
- Better nasal bioavailability for larger drug molecules as well as for smaller drug molecules.
- Nasal drug delivery system provides an alternative route for the Drugs which cannot be absorbed orally.

Disadvantages of nasal microspheres

- Dose is limited because of relatively small area available for the absorption of drug.
- Time available for drug absorption is limited.
- Diseased condition of nose impairs drug absorption.
- The nasal route of drug delivery is not applicable for all the drugs. [10]

Limitation

- The use of absorption enhancers to improve nasal drug delivery system.
- Toxicity which is yet to be established clearly.
- Limited surface area for Absorption when compared to GIT.
- Once the drug is administered through nasal route it cannot be removed.

MECHANISM OF NASAL ABSORPTION

The absorbed drug from the nasal cavity passes through the mucus layer. It is the first step in Absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs find difficulty to cross it. The principle protein of the mucus is mucin. It has the tendency to bind to the solutes and hinders diffusion of drug molecules. Structural changes in the mucus layer are possible as a result of environmental changes like change in pH, temperature. Many absorption Mechanisms were proposed earlier but only two mechanisms have been predominantly used, such as [11]

(a) First mechanism- It is also known as the paracellular transport. It involves an aqueous Route of transport but slow and passive. There is an inverse correlation between intranasal Absorption and the molecular weight of water soluble compounds. Drugs having molecular Weight greater than 1000 Daltons shows poor bioavailability.

(b) Second mechanism- It involves transport through a lipoidal route. It is also known as the Transcellular process. It is responsible for the transport of lipophilic drugs that show a rate Dependency on their lipophilicity. Drug also crosses the cell membranes by an active transport route via carrier-mediated means.

For example: chitosan, a natural biopolymer from shellfish is known to open the tight junctions between epithelial cells and facilitate drug transport.

PHYSIOCHEMICAL PROPERTIES OF DRUGS

Chemical forms

The chemical form of a drug is an important factor in determining absorption. For example, conversion of the drug into a salt forms can also alter its absorption. Huang et al (1985) studied the effect of structural modification of drug on absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L Tyrosine.

Polymorphism

Polymorphic nature of drug molecules is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes.

Molecular weight

A linear inverse correlation exists between the absorption of drugs and molecular weight up to 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Daltons. Absorption can be enhanced with the use of absorption enhancers [12]. Shape is also important that affects the absorption of drugs. Linear molecules have lower absorption whereas the cyclic – shaped molecules showed higher absorption.

Particle size

It has been reported that particle sizes greater than 10µm are deposited in the nasal cavity. Too fine particles i.e, below 5 µm should be avoided for nasal administration as there are chances of inhalation directly into the lungs.

Solubility and Dissolution rate

Drug solubility and dissolution rates are the predominant factor that governs nasal absorption from powders and suspensions [14]. The absorption profile is not only influenced by drugs solubility but also by the nature of pharmaceutical preparations. As the size of nasal cavity is small, the allowable volume of drug solution should be low for intranasal drug administration. Therefore, drugs poorly soluble in water or requiring high doses may affect the dissolution rate. The particles deposited in the nasal cavity should get dissolved prior to absorption. If a drug remains as particles or is cleared away, absorption of drug get hampered.

FORMULATION FACTORS

pH of the formulation

The pH of the nasal cavity and pKa of a particular drug should be considered in order to optimize systemic absorption. Nasal irritation can be minimized when products are delivered within the pH range of 4.5 to 6.5. Volume and concentration are important should also be considered. The delivery volume is limited due to the size of the nasal cavity [15]. An upper limit of 25mg/dose and a volume of 25 to 200 μl / nostril have been suggested in order to:

- Avoid irritation of nasal mucosa.
- Allows the drug to be available in unionized form for absorption.
- Sustains normal physiology of ciliary movement

Buffer capacity

Nasal formulations are generally administered in small volumes ranging from 25 to 200 μL . Hence, nasal secretions may alter the pH of the administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ [16].

Fig 1. Describing different pathways for reaching the brain after intranasal administration

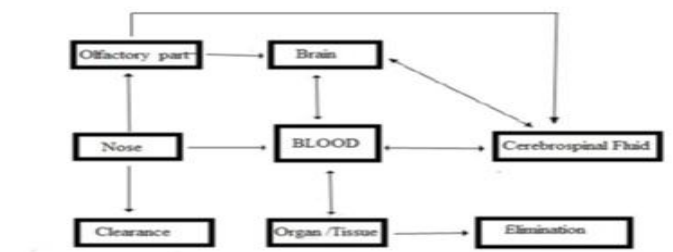
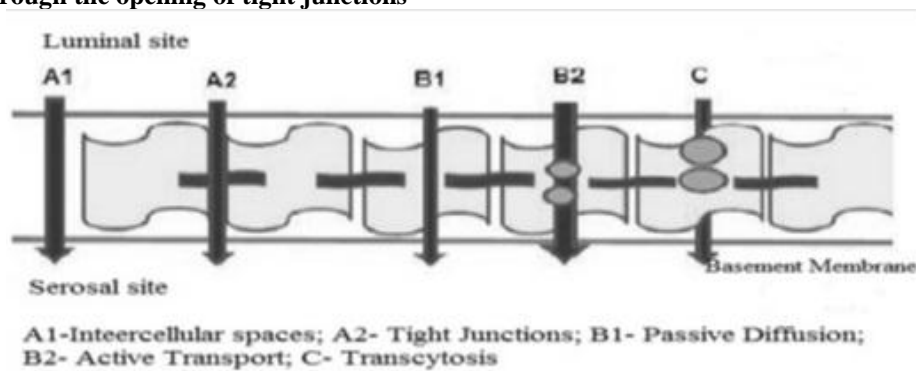


Fig 2. Transport through the opening of tight junctions



CONCLUSION

The nasal mucosa offers several advantages for controlled drug delivery. The mucosa is well supplied with both vascular and lymphatic drainage. First-pass metabolisms in the liver and presystemic elimination in the GI tract can be avoided. The area is well suited for a retentive device and has better patient compliance. The drug targeting to the brain should be evaluated for their

Viscosity

Higher the viscosity of the formulation greater is the contact time between the drug and the nasal mucosa thereby increases the time for permeation. At the same time, highly viscous formulations may interfere with the normal functions like ciliary beating, mucociliary clearance and thus alter the permeability of drugs [17].

Drug concentration, dose and dose volume

These are three interrelated parameters that affect the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments.

Role of absorption enhancers

Absorption enhancers are used when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation by amino peptidases. Absorption enhancers improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal blood flow, reducing mucus viscosity, and enzyme limitation [18].

safety and risk-benefit ratio for the patients. Currently the safety issue has been given great importance by the researchers during the research stage, and this issue will become critical when the drug is to be delivered is for a long term therapy. With the proper formulation and dosage form design, the permeability and the local environment of the mucosa can be controlled and manipulated to accommodate drug permeation. Nasal drug delivery is an

efficient alternate route for systemic delivery of orally inefficient drugs. It also offers non-invasive delivery of potent peptide and perhaps protein drug molecules. The intranasal route is an accessible alternative to parenteral routes. The need for safe and effective nasal permeation

and absorption enhancers is a major component for a promising future in the area of nasal drug delivery. It reduces systemic exposure and thus reduces the side effects.

REFERENCES

1. Ambikanandan Misra, Ganesh S, Aliasgar S. Drug delivery to the central nervous system: are view in. *J Pharmaceut Sci*, 26(2), 2003, 252-273.
2. Soni V, Chorasias MK, Gupta Y, Jain A, Kohli DV, Jain SK. Novel approaches for drug delivery to the brain. *Indian J. Pharm. Sci*, 66(2), 2004, 711-720.
3. Waterbeemd H, Camenisch G, Folkers G, Chretien JR, Raevsky O. Estimation of blood brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors. *J. Drug Targeting*, 6(2), 1998, 151-165.
4. Begley DJ. The blood-brain barrier: principles for targeting peptides and drugs to the central nervous system. *J. Pharm. Pharmacol*, 48, 1996, 136-146.
5. Begley DJ. Delivery of therapeutic agents to the central nervous system: the problems and the possibilities. *J Pharmacol. Therapeut*, 104, 2009, 29-45.
6. Garcia-Garcia E, Andrieux, K, Gil S, Couvreur P. Colloidal carriers and blood-brain barrier (BBB) translocation: A way to deliver drugs to the brain. *Int. J. Pharm*, 298, 2005, 274-292.
7. Pardeshi CV, Rajput, PV, Belgamwar VS, Tekade AR. Formulation, optimization and evaluation of spray dried mucoadhesive microspheres as intranasal carriers for valsartan. *J. Microencapsul*, 29, 2011, 103-114.
8. Illum L. Transport of drugs from the nasal cavity to the central nervous system. *Eur J Pharm Sci*, 11, 2011, 1-18.
9. Pardridge WM. Blood-brain barrier delivery. *Drug Discov Today*, 12 (1), 2007, 54-61.
10. Rosler A, Vandermeulen GWM, Kolk HA. Advances drug delivery devices via self-assembly of amphiphilic block copolymers. *Advance drug delivery reviews*, 53(2), 2009, 95-108.
11. Sivilotti L, Nistri A. GABA receptor mechanisms in the central nervous system. *Prog Neurobiol*, 2(1), 1991, 35-92.
12. Brem H *et al.*, Placebo controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *The Lancet*, 3(2), 1995, 1008-1012.
13. Bjorklund A, Dunnet SB, Dopamine neuron systems in the brain: an update. *Trends in Neurosci*, 3(2), 2007, 194-202.
14. MacKay JA, Deen DF, Szoka Jr. FC. Distribution in brain liposomes after convection enhanced delivery; modulation by particle charge, particle diameter and presence of steric coating. *Brain Res*, 1035, 2005, 129-135.
15. Mahoney MJ, Saltman WM. Controlled release of proteins to tissue transplants for treatments of neurodegenerative disorders. *J Pharm Sci*, 85(2), 1996, 1276-1281.
16. Benoit JP, Faisant N, Venier-Julienne MC, Menei P. Development of microspheres for neurological disorders: basics to clinical applications. *J Control Release*, 65(2), 2000, 285-291.
17. Swatantra KS, Kushwaha, Ravi Kumar, Keshari AK. Advances in nasal trans-mucosal drug delivery. *Journal of Applied Pharmaceutical Science*, 1(7), 2011, 21-28.
18. Dhakar CR. Non-invasive system drug delivery via nasal route: A Review. *AJPSP*, 2(1), 2011, 119-125.