WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 3, 697-707. Review Article ISSN 2277– 7105

NOSE TO BRAIN DRUG DELIVERY

Tayde M. A.[1] and Chavan S. R.[*1]

[*1]Department of Quality Assurance Technique, MGV'S Pharmacy College, Nashik.

Article Received on
10 Jan. 2019,

Revised on 31 Jan. 2019,
Accepted on 20 Feb. 2019

DOI: 10.20959/wjpr20193-14398

***Corresponding Author**
Chavan S. R.
Department of Quality Assurance Technique,
MGV'S Pharmacy College,
Nashik.

ABSTRACT

The present review focuses on nasal drug delivery system, in which drug deliver to brain via targeted nasal route. The nasal mucosa used for delivery and systemic administration of various drugs across the brain. In this system physiological barriers like blood-brain-barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) are avoided. Isotonic solutions of drug are usually preferred for nasal administration to avoid permeability problem. Nasal surface modification technology can be used as an excellent approach for nasal formulations.

KEYWORDS: Nasal drug delivery system, Mucosa, BBB, BCSFB, Isotonicity, Nasal surface modification.

INTRODUCTION

The concept of targeted drug delivery system has been originated from the perception of Paul Ehrlich, who proposed delivery of drug to be as a 'magic bullet'.[1] A number of aspects that are to be considered while designing targeted drug delivery systems include carrier, target and targeting ligand. Carrier is a drug vector, which isolate itself, transport and retain drug during its course, while elute or deliver it within or in the vicinity of area of interest. Targeting ligand is bounded to the specific pre-identified site. Drug delivery via nasal route has been practiced since ancient times for systemic effects. It is an excellent route for delivery of therapeutic compounds including biopharmaceutical as nasal mucosa has been considered as a potential administration route to achieve rapid and higher levels of drug absorption. Large surface area, porous endothelial membrane, high total blood flow, the avoidance of first pass metabolism, and ready accessibility are few of the major reasons for drug delivery across nasal mucosa.[2] Due to high degree of vascularization and permeability of the nasal mucosa, nasal route became popular for systemic delivery of drugs amongst researchers. Since, it is possible to target brain through targeted nasal drug delivery system.

Brain is a delicate organ, isolated from other circulatory systems and characterized by the presence of tight junctions of relatively impermeable endothelial cells, activity of enzyme, and active p-glycoprotein efflux transport mechanism. These formidable obstacles rendered many neuropathic unable to treat CNS disorders, since they cannot be delivered to the brain effectively. Delivery of drugs to the brain is a major challenge due to the presence to two physiological barriers that restricts the delivery of drugs to the CNS, the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB).[1,3]

1. NOSE ANATOMY AND PHYSIOLOGY

Nose is the important organ that filters particles from inhaled air. Inhaled air comes in contact with olfactory nerves which produces sense of smell. Nasal septum divides the nose into two symmetrical halves, each having opening through nostrils at the face and also extended posterior to the nasopharynx. Each symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished based on their anatomic and histological characteristics.[4]

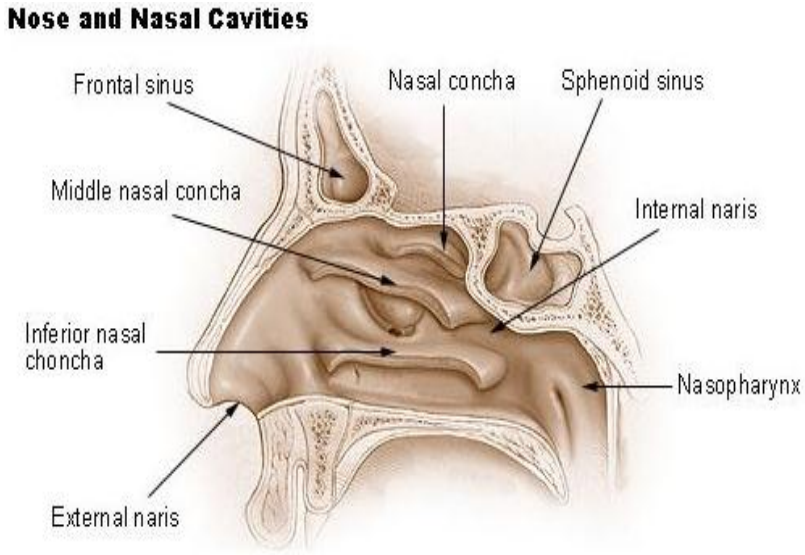

Figure 1: Anatomy of nose.

1.1 Vestibule: is not very highly vascularized and permeability of the drugs via this region is very poor.

1.2 Atrium: vascularization in this part of the nasal cavity is low, which results in moderate permeability of drugs.

1.3 Respiratory Region: This part of the nasal cavity is highly vascularized and therefore the permeability of drugs from this region is good.

1.4 Olfactory region: It is highly vascularized which results in high permeability of drug. In the olfactory epithelium, the nerve cells project into the olfactory bulb of the brain providing a connection between the brain and external environment and this connection is useful for the nose-brain drug transport.

2. INTRANASAL DRUG DELIVERY SYSTEM

Nasal applications for delivery to the brain have been pursued by the pharmaceutical industry since the 1980s. The nasal mucosa used for delivering and systemic administration of analgesics, sedatives, harmones, cardiovascular drugs, and vaccines, corticosteroid harmones. After nasal administration the concentration-time profiles are achieved which often similar to its intravenous administration and shows rapid onset of pharmacological activity.[5]

2.1 Advantages of intranasal drug delivery

- Increased patient compliance as needle free application is required and due to easy accessibility.
- Best for low molecular weight and lipophilic drugs as bioavailability is increased through nasal route for such drugs.
- Large absorption surface and high vascularization promotes rapid absorption and fast onset of action.
- Chemical and enzyme degradation of drugs (which is observed in GI tract) are avoided.
- Dose reduction is possible compared to oral route as first pass metabolism is avoided.
- Targeting drug to CNS via olfactory region is beneficial as BBB is avoided.

2.2 Limitations of intranasal drug delivery

- Nasal irritation may cause to some drugs.
- Absorption of drugs may affect due nasal congestion or allergies.
- Increase in molecular weight of drug delivery decrease the rate of drug delivery.
- Mucosal damage may occur due to frequent use of this route.
- The amount of drug reaches to targeted area is varied.

2.3 Barriers to intranasal drug delivery

2.3.1 Low bioavailability: Polar drugs generally low bioavailability, for low molecular weight drugs it is about 10% and not above 1% for large molecular weight peptides such as Calcitonin and Insulin.[2,6] The most limiting factor for absorption of polar drugs across the nasal mucosa is the low membrane permeability.

2.3.2 Mucociliary clearance: Mucociliary clearance can be another factor for low membrane transport, which causes general fast clearance of the administered formulation from the nasal cavity.

2.3.3 Enzymatic degradation: Possibility of an enzymatic degradation in the lumen of the nasal cavity or during its passage through epithelial barrier is the another contributing, but often less considered parametr to the low bioavailability of peptides and proteins.

2.3.4 P glycoprotein efflux: P-glycoproteins are a group of glycosylated membrane proteins found in epithelial cells of the body tissues. P-glycoproteins may hindered the drug absorption through efflux transport mechanism. Various factors are considered as barrier for bioavailability of drugs though nasal delivery systems listed in table 1.[7]

Table 1: Barriers in nasal drug product development.

Nasal barriers	Factors to be considered
I. Physiological barrier	
a. Nasal mucus	Viscosity, pH of mucus & drug-mucus interaction
b. Nasal epithelial barrier	Molecular weight, ionization constant & mode of transport
c. Mucociliary clearance	Nasal residential time & nature of dosage form
d. Pathophysiology	Volume of mucociliary clearance and permeability of epithelium membrane
e. Nasal metabolism	Nature of the molecules
f. Efflux transport system	Nature of drug molecule & duration of therapy
II. Physiochemical barriers	
Drug solubility & dissolution	Nature of dosage form, dose, pKa& polymorphism
b. Molecular weight & size	Less bioavailability with molecular weight more than 1000D
c. Compound lipophilicity	Affects the nose to blood & nose to brain absorption
d. pH and pKa	Unionized pH can aaffect absorption
III. Formulation factors	
Drug concentration, dose & volume	High concentration for better better bioavailability, maximum dose in Minimum vehicle (200µl >)
Osmolarity	Isotonic solution prevents epithelial damage & toxicity
Site of deposition	Viscosity, position of head, volume, delivery device

3. Factors influencing nasal drug absorption

3.1 Factors Related to Drug

3.1.1 Lipophilicity: Nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in barrier function of membrane. It is observed that with increasing lipophilicity drug absorption through nasal mucosa is also increased.[2,8]

3.1.2 Chemical Form: Modification of chemical form of drug can alter its absorption through nose. For example, conversion of drug into salt form can decrease its absorption.[2,9]

3.1.3 Polymorphism: Polymorphism may affect the dissolution rate and solubility of drugs and thus result in poor absorption through biological membranes. Hence, it is beneficial to study polymorphic stability and purity of drugs for nasal formulations.

3.1.4 Molecular Weight: For lipophilic drugs direct correlation observed between molecular weight and drug permeation, with increasing molecular weight drug permeation also increases. Whereas for hydrophilic drugs inverse relationship is observed.

3.1.5 Partition Coefficient and pKa: pH partition theory holds true in case of nasal absorption, that unionized species are absorbed better compared to ionized species.

3.1.6 Solubility and Dissolution Rate: For absorption of drug through nasal cavity, drug should be dissolved primarily.

3.2 Factors Related to Formulation

3.2.1 Physiochemical Properties of the Formulation

3.2.1.1 pH and Mucosal Irritancy: Mucosal irritancy can be avoided by adjusting the pH of nasal formulation within the pH range 4.5-6.5.[2,10] pH of the nasal formulation and absorption surface area of nose can affect drug permeation.

3.2.1.2Osmolarity: Isotonic solutions are generally preferred for nasal administration because other molarity (hypo or hypertonic) solution can affect the drug permeation through nose.

3.2.1.3Viscosity: High viscosity formulation increases the contact time between drug and nasal mucosa thereby result in increased time for drug permeation. Also highly viscous formulations interfere with the normal functions of nose.

3.2.1 Dosage form Used for Developing the Formulation

3.2.2.1 Nasal Drops: These are most simple and convenient system developed for nasal drug delivery. Main drawback of these formulations is the lack of dose precision. Also it is

reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

3.2.1.2 Nasal Sprays: Nasal sprays used for exact dose (from 25 to 200µl) delivery of the drugs due to availability of metered dose pumps and actuators. Choice of pump and actuator depend on the particle size and drug morphology. Powder spray may result in mucosal irritancy; thus, solution and suspension sprays are preferred over powder sprays.[2,11]

4. NEED FOR DEVELOPMENT OF NOSE TO BRAIN TARGETED DRUG DELIVERY SYSTEMS

Curing of CNS diseases occur by delivering drugs to the brain. Polar and large molecular weight compounds face problem of low permeability across endothelial membrane and also would be rapidly degraded by gastrointestinal enzymes or liver cytochromes, if orally administered. Thus, the transport of exogenous materials directly from nose-to-brain is potential route by avoiding BBB.

4.1 Mechanism

Some anatomical structures are involved in nose-to-brain transport. The pH of nasal mucus lies in the range of 5.5-6.5 and is moved by cilia present on the nasal mucosa.[4,12] Drug absorption in nasal cavity can be influenced by amount of nasal mucosa. It would act as first barrier for drugs administered intranasally and must cross before travelling between cells either paracellularly or transcellularly. First step in the absorption of drug from the nasal cavity is the passage through nasal mucus. Large and charged molecules are difficult to cross mucus membrane but smaller and uncharged molecules can easily pass. Mucin, is a protein present in the mucus and has ability to bind to the proteins and prevents their diffusion across nasal mucosa. Passage of drug molecules through the mucus takes place through several mechanisms is as follows:

4.1.1 Paracellular (aqueous route) transport, it slow and passive route. Large molecular weight compounds are difficult to cross by this mechanism.[5,12]

4.1.2 Transcellular (lipoidal route) transport or simple diffusion, involves transport of lipophilic drug molecule.[5,13]

4.1.3 Olfactory nerve pathway, drug uptake is by endocytic or pinocytic mechanisms and drug transportation takes place through intracellular axons (figure2).

Drugs would also cross the membrane via carrier mediated transport through the opening of tight junctions. An inverse log-log correlation was observed between nasal absorption and molecular weight of polar compounds. Larger molecular weight compounds (>1000 Daltons) face problem of poor bioavailability.[5,14]

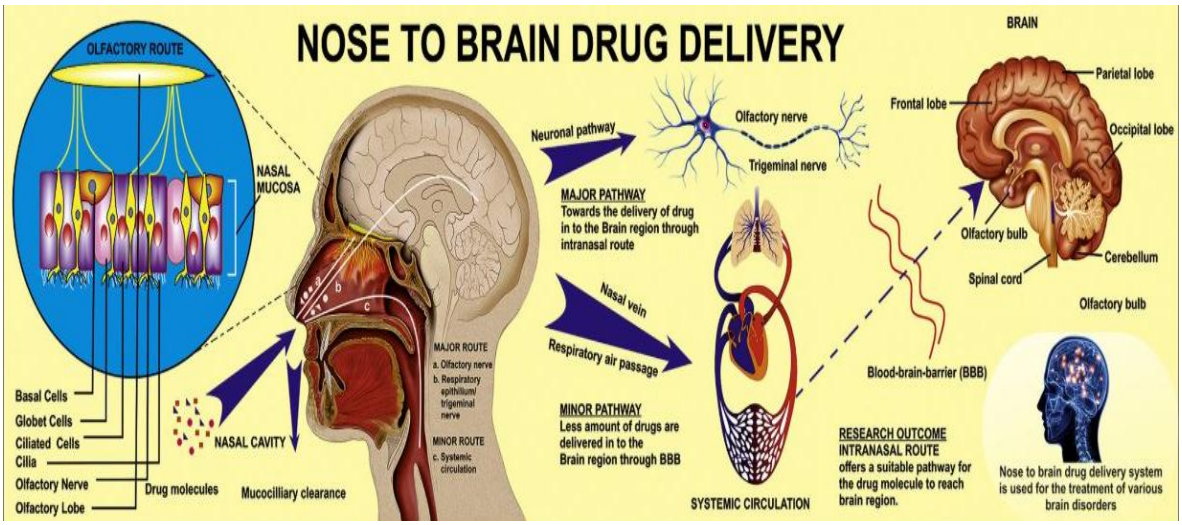

Figure 2: Mechanism for nose-to-brain drug delivery.

5. FORMULATION STRATEGIES FOR NASAL DRUG DELIVERY

5.1 Bioavailability of intranasal drug delivery

Various formulations strategies are made available to improve the bioavailability of nasal formulations. The basic mechanisms for enhancement of bioavailability are as follows:

- Incorporating nasal permeation enhancers to improve the absorption (e.g. cyclodextrins, fusidic acid derivatives, bile salt & surfactants, etc).
- Usage of enzyme inhibitors to eliminate nasal metabolism (e.g. bestatin,amastatin, boroleucine, etc).
- Formulation of mucoadhesive dosage forms to improve the nasal residential time (e.g. carbopol, polycarbophil, cellulose derivatives, lecithin & chitosan).
- Prodrug approach for optimizing favorable physicochemical properties.

Among this single approach or combination of two or more strategies is widely used to improve the bioavailability of nasal formulations. To achieve safety and efficacy of formulations variables like dose, frequency of dose, duration of treatment, toxicity of drugs and excipients, cost and condition of patients to be treated should be considered. Surface modification technology can be served as one of the excellent approach,[1] in which drug molecule can be coated by using different polymers so that it will not change the

physicochemical properties of drug molecule itself. Formulation strategies were determined by studying interaction between surface coating and biological system.

5.1.1 Chitosan surface modification: Chemical modification of Chitosan would not affect the basic physicochemical and biochemical properties of Chitosan and yield a novel derivative with enhanced properties. This is the main reason behind extensive use of this polymer in novel drug delivery.

5.1.2 PEG surface modification: Surface modification with PEG will overcome the limitations associated with polymer by adding new physicochemical properties to existing polymer.

5.1.3 Lectin surface modification: Lectin is a protein and obtained from plant sources such as tomatoes, jack bean and wheat germ. The selective biological surface affinity of lectin may be useful for direct nose-to-brain drug delivery.

6. Applications of intranasal drug delivery

6.1 In Situ-Based Gels for the Delivery of Anti-Parkinson Drugs

Researchers studied the effect of Levodopa loaded chitosan nanoparticles formulated by ionic gelation technique using sodium TPP (1mg/ml), incorporating into thermo-reversible gel prepared by using Poloxamer 407. Results indicated the increased drug absorption through addition of polycations on nasal mucosa by opening junction between tight epithelial cells and by delaying mucociliary clearan.[4,15] Ropinirole was delivered to brain through intranasal route by formulating mucoadhesive *insitu* gel using polymers chitosan and hydroxyl propyl methyl cellulose.[4,16]

6.2 In Situ Gels for the Delivery of Anti-Migraine Drug

In situ gel of Sumatriptan succinate was prepared in simulated nasal fluid using deacetylatedgellan gum (gelling agent). *Ex vivo* evaluation study showedhigher concentration of Sumatriptin in blood plasma and brain when administered intranasally as compared to its oral administration. The results also revealed that drug permeation takes place through olfactory pathway.[4,17]

6.3 In Situ Hydrogels for the Delivery of Anti-Alzheimer's Drugs

Huperzine A loaded gellan-gum based *in situ* gel was prepared by precipitation method. It is indicated that the AUC concentration of the Huperzine A in CSF after intranasal administration is 1.3 and 2 times as compared to it's intravenous and oral administration.[4,18] Curcumin loaded thermosensitive hydrogel was prepared using polymers Pluronic F121 and

poloxamer 188 for brain targeting. Formulated gel showed high retention time in nasal cavity as well as extended mucociliary clearance.[4,19]

6.4 In Situ Gels for the Delivery of Anti-Depressant Drug

Thermo-reversible gels for Doxepin was prepared using chitosan and glycerophosphate or poly(ethylene)glycol for nose to brain drug delivery. The *in-vivo*evaluation study of this formulation showed good antidepressant activity by lowering immobility time in Swiss albino mice.[4,20] Mucoadhesive thermo-reversible gel of Tramadol hydrochloride was prepared using chitosan nanoparticles. The formulation shows antidepressant activity by involving anti-oxidant like effects and significantly increased locomotor activity as well as body weight in rat model.[4,21]

6.5 In Situ Gels for the Delivery of Anti-Schizophrenia Drug

Paliperidone loaded *in situ*gel was formulated using carpbopol 934and hydroxyl propyl methyl cellulose for treating schizophrenia. Formulation showed good mucoadhesive property, high rate of permeation of drug through nasal mucosa.[4,22]

CONCLUSION

Nasal cavity has a large surface area and highly vascularized mucosa. Drugs are absorbed by the rich network of blood vessels pass through systemic circulation, thus it avoids first pass metabolism. Despite the potential of the nasal route, a number of factors limit the intranasal absorption of drug, especially protein and peptide drugs,are the mucus and epithelial barrier, mucociliary clearance and enzymatic activity. Rapid mucociliary clearance of drug formulations that are administered through the nasal cavity is thought to be an important factor for the low bioavailability of drugs administered intranasally. Increasing the residence time of the drug formulation in the nasal cavity, and hence prolonging the period of contact with the nasal mucosa, may found to improve drug absorption. The intranasal route of administration will probably have great future scope for the development of peptide preparations and other drugs those administered parenterally. Surface modification technology can be used excellent formulation strategy for nose to brain drug delivery.

REFERENCES

1. Patel, Z., Patel, B., Pardeshi, C., Nose to brain targeted drug delivery bypassing the blood-brain-barrier: an overview. Drug Invent Today, 2012; 4(12): 615-615.

2. Jadhav, K., Gambhire, M., Shaikh, I., et al. Nasal drug delivery system-factors affecting and applications. Current Drug Therapy, 2007; 2(1): 27-38.
3. Alam, M.I., Beg, S., Samad, A., et al. Strategy for effective brain drug delivery. Eur. J. Pharm. Sci., 2010; 40: 385-403.
4. Blessing, A.A., In situ-based gels for nose to brain drug delivery for the treatment of neurological diseases. Pharmaceutics J., 2018; 10(40): 1-17.
5. Parvathi, M., Intranasal drug delivery to brain: an overview. IJRPC, 2012; 2(3): 889-895
6. Illum, L., Nasal drug delivery: New developments and strategies. Drug Discov Today, 2002; 7(23): 1184-1189.
7. Bhise, S.B., Yadav, A.V., Avachat, A.M. et al. Bioavailability of intranasal drug delivery system. Asian Journal of Pharmaceutics, 2008; 201-215.
8. Corbo, D.C., Liu, J.C., Chien, Y.W., Characterization of the barrier properties of mucosal membranes. J. Pharm. Sci., 1990; 79: 202-206.
9. Huang, C., Kimura, R., Nassar, A., Hussain, A., Mechanism of nasal drug absorption of drug II: absorption of L-tyrosine and the effect of structural modification on its absorption. J. Pharm. Sci., 1985; 74: 1298-1301.
10. Arora, P., Sharma, S., Garg, S., Permeability issues in nasal drug delivery. Drug Discov Today, 2002; 7(18): 967-975.
11. Ishikawa F, Katsura M, Tamai I, Tsuji A. Improved nasal bioavailability of elcatonin by insoluble powder formulation. Int. J. Pharm., 2001; 224: 105-114.
12. Aurora, J., Development of nasal delivery systems: a review. Drug Deliv Technol., 2002; 2(7): 1-8.
13. Dodane, V., Khan, M.A., Merwin, J.R., Effect of chitosan on epithelial permeability and structure. Int. J. Pharm., 1999; 182: 21-32.
14. Rassu, G., Soddu, E., Cossu, M., Gavini, E., et al. Particulate formulations based on chitosan for nose-to-brain delivery of drugs. A review. J. Drug Deliv. Sci. Technol., 2016; 32: 77-87.
15. Sharma, S., Lohan, S., Murthy, R., Formulation and characterization of intranasal mucoadhesive nanoparticulates and thermo-reversible gel of levodopa for brain delivery. Drug Dev. Ind. Pharm., 2014; 40: 869-878.
16. Khan, S., Patil, K., Bobade, N., Gaikwad, R., Formulation of intranasal mucoadhesive temperature-mediated in situ gel containing ropinirole and evaluation of brain targeting efficiency in rats. J. Drug Target, 2010; 8: 223-234.

17. Galgatte, U., Kumbhar, A., Chaudhari, P., Development of in situ gel for nasal delivery: Design, optimization, in vitro and in vivo evaluation. Drug Deliv., 2014; 21: 62-73.
18. Tao, T., Zhao, Y., Yue, P., Dong, W., Chen, Q., Preparation of huperzine A nasal in situ gel and evaluation of its brain targeting following intranasal administration. *Yao Xue Xue Bao*, 2006; 41: 1104-1110.
19. Chen, X., Zhi, F., Zhang, X., Enhanced brain targeting of curcumin by intranasal administration of a thermo-sensitive poloxamer hydrogel. J. Pharm. Pharmacol., 2013; 65: 807-816.
20. Naik, A., Naik, H., Formulation and evaluation of thermo-sensitive biogels for nose to brain delivery of doxepin. Biomed Res. Int., 2014; 10.
21. Kaur, P., Garg, T., Vaidya, B., Prakash, A., Brain delivery of intranasal in situ gel of nanoparticulated polymeric carriers containing antidepressant drug: Behavioral and biochemical assessment. J. Drug Target, 2015; 23: 275-286.
22. Sherja, A., Londhe, V., Development and evavaluation of pH-responsive cyclodextrin-based in situ gel of paliperidone for intranasal delivery. AAPS Pharm. Sci. Tech., 2018; 19: 384-394.