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Brain Targetting through Intranasal Route

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Abstract: The blood brain barrier (BBB) represents one of the strictest barriers of in vivo therapeutic drug delivery. The barrier is an restricted exchange of hydrophilic compounds, small proteins and charged molecules between the plasma and central nervous system (CNS). For decades, the BBB has prevented the use of many therapeutic agents for treating Alzheimer's disease, stroke, Brain tumour, head injury, depression, anxiety and other CNS disorders. Various techniques and Attempts were made to deliver the drug across the BBB such as modification of therapeutic agents, Altering the barrier integrity, carrier-mediated transport, invasive techniques, etc. However, opening the barrier by such means allows entry of toxins and undesirable molecules to the CNS, resulting in potentially significant damage. Many advanced and effective approaches to brain delivery of drugs have emerged in recent years. Intranasal drug delivery is one of the focused delivery options for brain targeting, as the brain and nose compartments are connected to each other via the olfactory route and via peripheral circulation. In this review we discuss the effects of microspheres and other Bioadhesive drug delivery systems on nasal drug absorption. Drug delivery systems, such as microspheres, liposomes, Microemulsion, Nano emulsion and gels have been demonstrated to have good Bioadhesives characteristics and that swell easily when in contact with the nasal mucosa.

Keywords: Central nervous system, Alzheimer's disease, Stroke, Intranasal delivery, Microspheres, Microemulsion, Liposomes.

Introduction:

Nasal drug delivery is used for various kinds of diseases. It is not only used recently but it recognised form of treatment in the Ayurvedic system of Indian medicine called "*nasal karma*".[1] in recent year growing interest has focused on the use of nasal route for systemic delivery & Brain targeting. Drug which undergoes first pass metabolism to avoid this and increases there bioavailability of drug nasal route is preferred[2]. It is useful for the drug which are active at low doses & show very less oral bioavailability such as Protein and peptide[3].central nervous system diseases such as Epilepsies, meningitis, migraine, Parkinson diseases, Alzheimer diseases has difficulty In targeting because of the transport through Blood Brain Barrier[4]. From literature it shows that such diseases can be treated by transporting exogenous material to brain by nose or it's an effective route by passing BBB[5]. The result of concentration time Profile of intranasal administration drug is similar to the Intravenous route[6]. The pathway employed for the delivery of particular drug from the nose to brain is highly dependent on various factors, such as existence of specific receptor on the olfactory neurons, the lipophilicity and molecular

weight of the drug[7]. Intra nasal delivery is non invasive& painless delivery and it does not required sterile preparation & it is easy method of drug administration for patient or physician. The nasal route offers improve delivery for "non-Lipinski" drug[8]. Lipophilic drug can easy cross BBB by traveling throw Transcellular pathway. Hydrophilic drug transport throw paracellular pathway so they have very less chance to pass BBB. Polar molecule have very less chance to pass from respiratory region to blood stream so they have some chances to reach brain by passing or travelling throw olfactory mucosa in nose[9]. Although many novel nasal product for systemic delivery on various diseases are launched in market but still no drug exploiting the nasal route to treat CNS diseases. Development of drug delivery throw nose to enable rapid & effective concentration in Brain is challenges for Researchers[7].

Advantages of nasal drug delivery:[10,11,12]

1) Drug degradation that is observed in the gastrointestinal track is absent.
2) Hepatic first pass metabolism is avoided.
3) The nasal bioavailability for smaller drug molecule is good.
4) Studies so far indicates that the nasal route is an alternative to parenteral route, especially for protein's and peptide drug.
5) Convenient for the patient especially for those on long term therapy, when compared with parenteral medication.
6) Polar compound exhibiting poor oral absorption may be particularly studies for this route of delivery.
7) Large nasal mucosa surface area for dose absorption.
8) Ease of administration, non-invasive.
9) Lower dose reduced side effects.
10) Self-administration.

Limitations:[13,14,11,12]

1) Delivery is expected to decreases with increasing molecular weight of drug.
2) Mucosal damages may occurs due to frequently use of intra nasal route.
3) Very specific amount i.e. 25-200µ can be delivered throw intra nasal route.
4) Ciliary movement after the drug permeability.
5) Difficult to administered drug in pathological condition such as nasal congestion due to cold or allergic reaction.
6) Some drug cannot administered throw this route because they causes nasal irritation.
7) There could be mechanical loss of dosages form into the other part of respiratory track like lungs because of the improper technique of administration.
8) The histological toxicity of different type of penetration enhancer used is not clearly known.

Nasal anatomy and physiology:

The main role of nose are olfaction, regulation of humidity & temp of inhaled air and removal of microorganism or particulate matter from inhaled air. By using computed tomography scan the total surface area & volume of nasal cavity is measured as 150 cm^2& 13.0 ml respectively[15]. The nasal cavity is a space suited above the oral cavity & hard palate and below the skull base & intracranial compartment the nasal septum consist of cartilage in its front end and bone towards back of the nose. The perpendicular plate of the ethmoid bone, vomer bone & maxilla bone these three gives nasal septum. The left & right nasal cavity becomes continuous in the back if nose via the opening to the nasopharynx. Nasopharynx contain a collection of centrally located lymphoid tissue called the adenoid nose is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils & extending to the nasopharynx. Nasal cavity is lined with mucus layer and hair.[16] composed of 95% water, 2% mucin, 1% salt, 1% other proteins such as albumin, immunoglobin, lysozymes &lactoferrin, & 1% lipid[17].

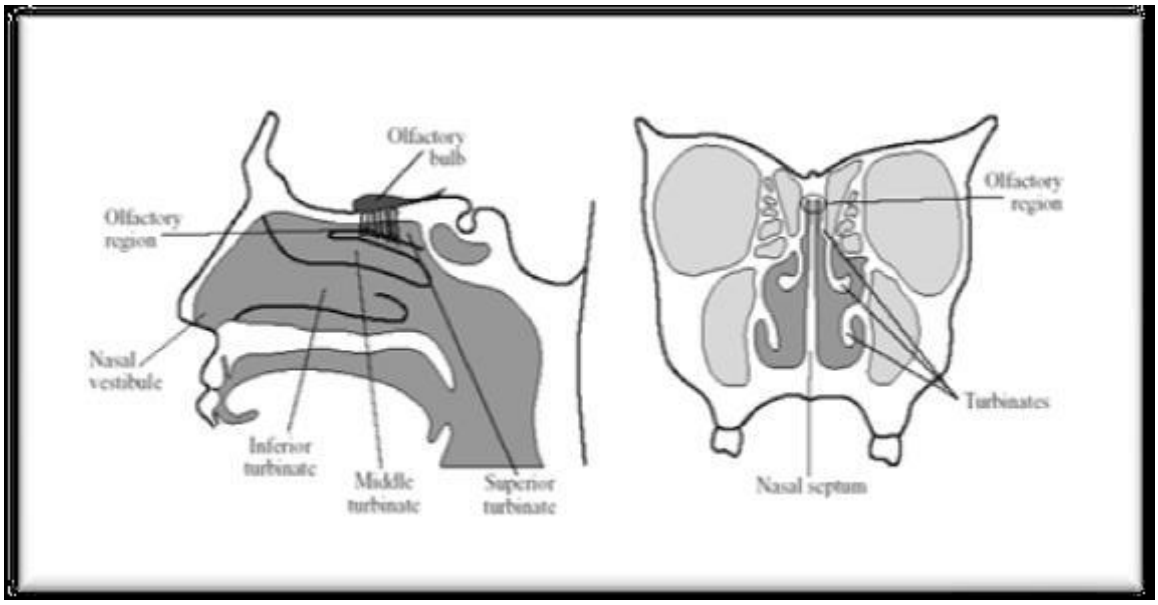

Fig.1. Nasal anatomy & physiology[18]

Respiratory epithelium &mucociliary clearance:

It composed of four types of cells:

- **Non-ciliated**
- **Ciliated columnar cell**
- **Basal cell**
- **Goblet cell**

This cell prevent drying of mucosa by trapping moisture. These cell facilitated active transport processsuch as exchange of water & ions between cell & motility of cilia.about 15-20% of respiratory cells covered with layer of lomg cilia. Mucus present over epithelial cell causes mucociliary clearance. Mucous moves only in one direction from the anterior to posterior part of nasal cavity to the nasopharynx[19,20,21,22]. Mucous secretion gives immune protection against inhaled bacteria or virus. Mucous has water holding capacity, it exhibit surface electrical activity, it also act as transport & adhesive for particulate matter towards nasopharynx[23].

Olfactory region:

In human olfactory region is located on the roof of the nasal cavities, just below the cribriform plate of the Ethmoid bone, which separates the nasal cavities from the cranial cavity[22]. The olfactory epithelium predominantly contain three cell types:

1. Olfactory neural cells,
2. Sustenticular (supporting) cells,
3. The basal cells

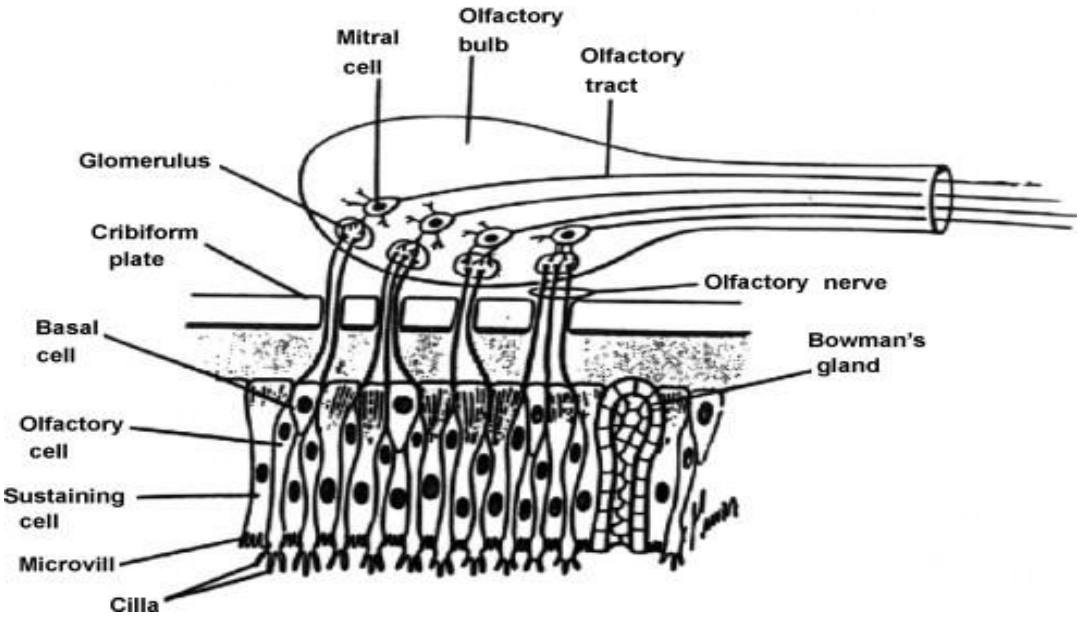

Fig.2. Olfactory region of nose[24]

Olfactory neuron are interspaced between supporting cell. This areunmglinated cells[25]. They originate at the olfactory bulb in the CNS & terminate at the apical surface of the epithelium. The cilia contain chemical detector, it will get activated by odour and cause depolarisation by ion gated channel or C-GMP pathway[26]. beneath the epithelium layer lamina propria is present. Which contain blood supply, mucous secretion acinar glands, nasal lymphatic, & neuronal supply that consist of olfactory axon bundles, autonomic nerve fibre and maxillary branch of trigeminal nerve[27].Filia olfactory are unique feature in that around twenty axon are partitioned by Schwann cell into fascicles. This feature 10-15nm size space between axon that act as ionic reservoir for action potential propagation.Mesaxons are pores in Filia olfactory that allow passage of extracellular fluid into neuronal bundle structure. The transport of drug across the nasal membrane & into blood stream may involve passive diffusion of drug through the pores in nasal mucosa, including blood supply, nerve supply or some form of non-passive transport[28].

Barrier for nasal drug delivery:

1. **Enzymes barrier:** nasal mucosa contain various enzymes such as cytochrome P450- dependent monooxygenase, carboxyl esterase and amino peptidase. Such as enzymes present in mucosa provides a pseudo-first-pass effect[29]. The low transport of protein & peptide across nasal membrane is due to the enzymatic degradation of molecule either due to enzyme in nasal cavity or during passage across the epithelial barrier. exopeptidase cause cleavage of peptide at their n & c terminal &endopeptidase cause cleavage by attacking interval peptide bond[17].
2. **Mucociliary clearance:** The fast clearance of formulation through nasal cavity is due to the mucociliary clearance. Particles entrapped in nasal mucosa is get transport & cleared from body. This both combined action at mucous & cilia is called as mucociliary clearance[30]. It has shown that liquid & powder formulation which does not contain bioadhesion having half-life clearance is 15-30 mins[23,31].themucociliary clearance is directly praporshnal to residence(contact) time between drug and epithelial cells[31]. The clearance may be improve by adding Bioadhesives material in formulation in less ciliary part i.e. anterior part of nose[32,33].
3. **Protective barriers:** the nasal membrane is physical barrier & the mucociliary clearance is a temporal barrier to drug absorption across nasal epithelium[34].
4. **Low bioavailability:** lipophilic drug can easily get through intranasal route. Pharmacokinetic profile of lipophilic drug administered through intravenous route is similar to intranasal route. Bioavailability

approaching 100% e.g. fexofenadine from the microemulsion applied intranasal route then T_{max}observed within 5min at 1mg/kg dose and absolute bioavailability was about 68% compared to intravenous administration[35]. Bioavailability of polar drug is generally low about 10% the important factor limiting the polar drug absorption having large molecular size and their low permeability through membrane. Polar drug having molecular weight less than 1000Da will generally pass through membrane[36]. Permeability of such polar drug can be improved by adding absorption enhancing agent used for intranasal absorption include surfactant (laurenth-9, sodium lauryl sulphate) bile salt, bile salt derivatives, fatty acid, phospholipid, cationic compound like chitosan & its derivatives , poly-L-arginine, poly-L-lysine[37].

Formulation aspects for Intranasal drug delivery-

1. **Nanoparticles:** in order to improve the absorption of nanoparticle in the Brain following nasal administration a novel protocol to conjugate biorecognitive ligand-lectins to the surfaces of poly (ethylene glycol), poly (lactic acid), (PEG-PLA), nanoparticles was established[38]. An approach to enhance nasal adsorption of nanoparticles is the surfaces modification with biorecognitive ligand such as lectins. Lectins are more probably used because it is non-immunological origin, specially recognise surface molecule[39,40]. wheat germ agglutinin coupled with PLA-PEG nanoparticles was about 2 folds in different Brain tissues compared with that of coumarin incorporated in unmodified ones. Ulexcuropeus agglutinins I (UEAI) conjugating also elevated the brain targeting efficiency of nanoparticles. UAE-I modified nanoparticles indicated their higher affinity to the olfactory mucosa than to the respiratory one. So it becomes the potential carrier for brain drug delivery[38]. Odorranolectin was recently identified as the smallest lectins with much less immunogenicity than other member of lectins family. Odorranolectin nanoparticles could be potentially used as carrier for nose to brain drug delivery, especially macro-moleculacular drug, in the treatment of CNS disorders[41].
2. **Micro-sphere approach:** in vaccines delivery chitosan micro-sphears prepared in the presence of selected immunomodulatorpluronic block copolymer F127. The bordetellabronchiseptica multiple antigen containing dermonecrotoxins (BBD), a virulent factor leading to atrophics rhinitis in swine was loaded in chitosan microspheres F127. In vivo studies in mice shows that the mice immunized with BBD-CM_S 1F127 showed lighter BBD specific IgA antibody response in nasal wash saliva and serum that mice immunized with BBD CMs alone[42]. In vitro drug release studies from microsphere were achieved according to USP XXIV nasal administration of microparticles to rat obtained by spray drying can be perform to obtained the selective CNS targeting of anti-ischemic drugs[5].
3. **Nasal Gels:** Zedovudine is transferred to brain via intra nasal route through olfactory route by using thermo reversible gelling system. The nasal gel formulation was prepared by dissolving zidovuidine in pH 5.5 phosphate buffer solution comprising of 20% polyethylene oxide/polypropylene oxide (Polaxomer 407®, PLX). Thermorevesible gelling agent and 0.1 % n-tridecyl-β-D-maltoside (TDM) as permeation enhancer. The CSF and brain Zedovudine level achieved after intranasal of gelling formulation where approximately 4.6 to 5.6 times greater than those attained after IV injection[43]. In administration of huprazine-A nasal inside gel significantly increased distribution of hup-A into rat brain tissue especially into cerebrum and hippocampus which should be the target areas of hup A and enhance the brain targeting of hup-A[44].
4. **Microemulsion and Nano emulsion:** To enhance the solubility and bioavailability of poor absorbable fexofenadine microemulsion system composed of oil, surfactant &co-surfactant was developed for intranasal delivery. oil phase used in the emulsion is lauroglycol 90, labrasol as surfactant and plurololeique 1149 or its mixture with PEG 400 (1:1) as co-surfactant result suggested that this micro emulsion formulation could be used as an effective intranasal dosage form for rapid onset delivery of fexofenadine[35.]in emergency treatment of status epilepticus ethyl laureate based micro emulsion may be a useful approach for rapid onset delivery of diazepam[45.]Mucoadhesive Nano emulsion of Resperidone indicated more effective and best brain targeting approach[9].
5. **Dry powder:** intranasal vaccination represent attractive non-invasive and alternative to needle based injection and provide superior protection at mucosal surface. Powder formulation of whole inactivated influenza virus provide a novel intranasal delivery platform. The powder formulated vaccine elicited a

significant serum antibody response in rats that was at least as strong as that provided by the liquid vaccine administration Intravenous or intramuscular injection.[46]

6. **Liposomes:**this are soft vascular structure formed by soft-assembly of phospholipid which are the same material as cell membrane. They can be formed in many shaped & size depending upon lipid composition. Liposomes are often used as non-viral carrier for DNA delivery because of their dynamic properties of cellular membrane that interact with the biological environment[47]. Liposomes are also coated with several thousand strands of polyethylene glycol (PEG) to extend the circulation times in blood. About 1-2% of the PEG polymers tips are conjugated with a targeting monoclonal antibody which act as a molecular Trojan horse, specific to brain receptor. This types Trojan horse liposomes is also called PEG gylatedimmunoliposomes. The molecular Trojan horse then binds to the receptor on the BBB and brain cell membrane, triggering receptor-medicated transcytosis of the liposomes across the BBB and endocytosis into brain cell[48].

Therapeutic application of nasal drug delivery:

1. **Intranasal delivery of cells to brain:** the success of cell based therapy for neurodegenerative disorders depend on therapeutic properties of the cell type, on the method and safety of administration, on the amount of cells delivered to the site of injury and finally on the avoided of excessive incorporation of the therapeutic cell into other organ and system. This methodologically, transplantation may raise problem not only because of graph rejection as a result of immunological response to the transplant[49,50,51.]the intranasal administration of mesenchyamal stem cells and glioma cells to the brain of rodent and the enhancement of cell delivery with hyaluronidase. This biological pathway of cell migration from the nasal mucosa to the brain thus provide an opportunity for development of cell delivery method for therapeutic and experimental use in treating brain tumour model[52.]
2. **Rapid delivery of Metoclopramide Hydrochloride:** it is potent anti-emetic effective in the treatment and vomiting associated with migraine, cancer therapy, pregnancy. It is well absorb orally and shows peak plasma concentration in 1 to 2 hours after oral dose. But due to first pass metabolism of metoclopramide hydrochloride its plasma concentration and bioavailability showing variable values between 32% to 98%[53,54.]In this study nasal formulation of metoclopramide hydrochloride were developed to increase the extent of absorption through bypassing of hepatic first pass metabolism and to develop alternative antiemetic therapy. Nasal bioavailability of this drug may be improved aid of absorption promoters which include anionic enhancers such as bile salt as well as new cationic enhancers such as chitosan, protamine and poly-L-arginine[55].The highest promoting effect was observed with the bile salt sodium, deoxycholate where about 92% of the drug was absorb in 25 min. from the rat nasal cavity and the Kapp showed more than two fold increase as compare to controlled (from 0.045 to 0.1017 min^{-1})[37].
3. **Insulin like growth factor-I (IGF-I):** intranasal administration is a non-invasive method of bypassing the BBB and delivers IGF-I to the brain directly from nasal cavity along the pathway that seems to be associated with the peripheral olfactory and trigeminal system[56].IGF-I has been proposed as a treatment for stroke. However, it does not efficiently cross the BBB. Intracerebroventricular injection of IGF-I has been shown to offers protection against cerebral ischemic damage in rats although this invasive method may not be practical in humans. Treatment of middle cerebral artery occlusion (MCAO).treatment was initiated 10 minute after the onset of MCAO and then again 24 hrs. And 48 hrs. Later. Intranasal dosing of 75µg IGF-I(225µg total IGF-I over 48hours) significantly reduced corrected infarct volume by 60% Vs. control ($P< 0.001$) and hemispheric swelling by 45.6% Vs. control($P<0.05$).neurologic function assessed by the postural reflex, flexor response and adhesive tape test was also improved by intranasal IGF-I as compared to control[57].
4. **Intranasal Insulin delivery:** the history of insulin was first discovered in 1992 and was successfully used for treating diabetes melittus[58].although the oral route is preferred for administration of drug, particularly those required in chronic therapy, it is not feasible for the systemic delivery of most peptide and protein drugs including insulin[59-62]. Due to the poor oral availability insulin is now a days administered parenterally[63]. There are humorous disadvantages to injectable insulin therapy. Poor patient compliance due to pain and discomfort during self-injection, particularly if multiple daily injections are required and it can be problematic[64,65].The difficulties in achieving normal physiological

profile of insulin by injectable therapy has led to the investigation of alternative, non-parenteral, route for the delivery of insulin in an attempt to improve glycemic control[66]. There are number of other non-parenteral route other than oral route which have been investigated for the systemic administration of peptide and protein drug such as transdermal, ocular, buccal, rectal, vaginal, pulmonary and nasal route. Out of all this route intranasal route is more viable and effective[67-69]. Sephadex (dextran microsphere)was shown to promote nasal insulin absorption in rats, although DEAE-sephadex(DEAE-dextran microsphere)was ineffective which correlated with the in vitro release characteristic of insulin from microsphere system.dextran microsphere which were coated with insulin were shown to be more effective in terms of promoting insulin absorption in rats than insulin-loaded microsphere[70]. By using chitosan polymer as absorption enhancer the different percentage of chitosan is used for making formulation for intranasal administration.0.5%and 1.5%chitosan was used this shows increase in bioavailability through intranasal administration of insulin[71].

Conclusion:

Intranasal administration of therapeutic agents (i.e., drug delivery via the nose) offers several advantages over oral, intravenous, and other routes of administration. Drugs can be rapidly absorbed through the large surface area of the nasal mucosa. It reduces systemic exposure and thus reduces the Side effects. This route also has shown clinical significance by reducing Adverse effects and Toxic Effects due to decrease in dose. Although lot more information regarding this route has to be discovered to make drug delivery through this route more effective and effecious than other route. It is an challenge for researcher to make this susceptible to patients.

References

1) Chien Y.W., Chang S.F. Intranasal Drug Delivery for systemic medications.Crit Rev Ther Drug Carr Syst 1987;4:67-194
2) Paun J.S., Bagada A.A., Raval M.K.., Nasal Drud Delivery-As An Effective Tool For Brain Targetting-A Review.,International Journal Of Pharmaceutical And Applied Sciences/1(2)/2010;43-55
3) Jadhav Kisan R., GambhireManoj N., Ishaque M. ShaikhManoj N., kadamVilarsrao J. and. PisalSambhaji S, Nasal Drug Delivery System Factors Affecting and Applications, Current Drug Therapy, 2007,2,27-38
4) Pardride WM. Non-Invasive Drug Delivery to human brain using endogenous blood-brain barrier transport systems.pharmaceutical sciences technology today 1999;2:49-59
5) Illum L. Transport of drug from the nasal cavity to the central nervous system. European Journal of Pharmaceutical Sciences 2000;11:1-18.
6) Hussain AA. Intranasal Drug Delivery. Advanced Drug Delivery Reviews,1998;29:39-49.
7) SandorHorvat, Targetting Pharmacons To The Brain Via The Nasal Pathway,2009,1-17.
8) Johanson P.H., Quay, S.C., Advances in nasal drug delivery through tight junction technology. Expert opinion.Drug Delivery 2,2005,281-298.
9) Kumar M., Misra A., Babbar A.K., Mishra A.K., Mishra P., Pathak K.. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone,Int. J. pharm.358(1-2)(2008)285-291.
10) Aulton M.E. “Pharmaceutics-The of Doasge Form Design” Churchill Livingstone.,494,2002, Krishnamoorthy R, Ashim k. Mitra, Prodrugs for nasal drug delivery. Advanced Drug Delivery Reviews 1998;29:135-146.
11) Sam E, Jeanjean AP, Maloteaux JM, Verbeke N. Apomorphin pharmacokinetics in parkinsonism after intranasal and subcutane application. Eur J Metab Pharmacokinetic.1995;209(1):27-33.
12) Bahl CR, Pamplaskar HK, Sileno AP, Romeo VD. Effects of Physicochemical properties and other factors on systemic nasal drug delivery, Advance Drug Delivery review.1998;(29):89-116.
13) Kadam SS, Mahadik KR, Pawar AP, Paradkar AR. Tranasal Delivery of Peptides- a Review. The East. Pharm. 1993;47-49.
14) Hirai S, Yashik T, Mima H. Effect of Surfactant on nasal absorption of insulin in rats. Int. J. Pharm.1981;9:165-171.

15) Menache MG, Hanna LM, Gross EA, Lou SR, Zinreich SJ, Leopold DA, Jarabek AM, Miller FJ. Upper respiratory tract areas and volumes of laboratory animals and humans:consideration of dosimentry models. J Toxicol Environ Health 1997;50:475-506.
16) Justin H. turner, MD and Jayakar V. Nayak.MD PhD, Nasal anatomy, America rhinoogical society.
17) Kaliner M., Marom Z., Patow C., Shelhamer J, Human respiratory mucus, J. allergy Clin. Immunol.1984, 73,318-323.
18) Singh Anita, SatheeshMadhav N.V;NASAL CAVITY: A PROMISING TRANSMUCOSAL PLATFORM FOR DRUG DELIVERY AND RESEARCH APPROACHES FROM NASAL TO BRAIN TARGETTINGJournal of Drug Delivery & Therapeutics;2012, 2(3): 22-33.
19) Alpesh M., Snjezana S, LisbethI.Nanoparticles for direct nose to brain delivery of drugs.1982;71-97.
20) Schipper et al. The nasal mucociliary clearance: relevance to nasal drug delivery. pharma. Res. 1991;7:807-814
21) JungingerBiosdhesive polymer system for peptide delivery.Acta.pharma.Tech.1990;36:110-126.
22) Chien YW, Su KS, and Chang SF. Anatomy and Physiology of the nose.In nasal Systemic Drug Delivery: Drugs and the Pharmaceutical Sciences. New York: Marcel Dekker;1989;1-26.
23) Lee, V.H.,. Enzymatic barriers to peptide and protein absorption. Crit. Rev. Ther. Drug Carrier Syst.5, 1998,69-97.
24) ChaudhariRakhi, Goswami Lakshmi, Nasal Route: A Novelistic Approch For Targetting Drug To CNS, International Research Journal of Pharmacy2013, ISSN 2230-8407; Pg no. 59-62.
25) Adams GL,Boies LR, Hilger PA, Boies's Fundamentals of Otolaryngology a Textbook of Ear, Nose and Throat Diseases. Saunders, Philadelphia;1989:177-195.
26) Gartner LP, Hiatt JL. Color Atlas of Histology. Lippincott Williams & Wilkins, Philadelphia;2000.
27) Brand G. Olfactory/trigeminal interactions in nasal chemoreception. NeurosciBiobehav Rev. 2006;30:908-917.
28) Talegoanka S, Mishra PR, intranasal delivery: An approach to bypass the blood brain barrier. Indian journal of pharmacology.2004;36(3):140-147.
29) Soane RJ, Frier M, Perkins AC, Jones NS and Davis ss. Illum L Evaluate ion of the clearance characteristics of bioadhesive systems in human.Int J Pharm. 1999;178:55-65.
30) Illum L, Mathiowit ZE and Chickering DE. Bioadhesive formulations for nasal peptide delivery:fundamentals, Novel Approch and Development. New York: Marcel Dekker. 1999;507-539.
31) Merkus FW, Verhoef JC, Schipper NG, Marttin E. 1998. Nasal mucociliary clearance as a factor in nasal drug delivery.Adv Drug Deliv Rev.29:13-38
32) Kublik H, VidgrenMT.Nasal delivery system and their effects on deposition and absorption. Advance Drug Delivery Review. 1998;29:157-177.
33) Harris AS, Nilsson IM, Wagner ZG, Alkner U, Intranasal administration of desmopressin. J Pharm Sci. 1986;75(11):1085-1088.
34) Lee V H L. Enzymatic barriers to peptide and protein nose to brain pathway for psychotropic peptides: CRC Crit Rev Ther Drug Carrier Sys 1998:5:69-97.
35) Hong-Mei Piaoa, PrabagarBalakrishnana, Hyun-Jong Choa, HyunjunKimb, You-Sun Kimb,Suk-Jae Chunga, Chang-Koo Shima, Dae-DukKima,Preparation and evaluation of fexofenadine Microemulsions for intranasal Delivery,International Journal of Pharmaceutics,(2010); 309–316.
36) Mc martin C, Hutchinson LE, Hyde R, Peter GE, Analysis of structural requirments for the absorptions of drugs and macromolecules from nasal cavity. J. Pharm. Sci. 1987;76:535-540.
37) Davis SS, Illum L. Absorption Enhancers for Nasal Drug Delivery. Clin. Pharmacokinetic; 2003;42(13); 1107-1128.
38) XiaolingGaoa, WeixingTaoa, Wei Lua, QizhiZhanga, Yan Zhangb, XinguoJianga,,ShoukuanFub;Lectin-conjugated PEG–PLA nanoparticles: Preparation and brain delivery after intranasal administration; Biomaterials 27 (2006) 3482–3490.
39) Sharma A, Sharma S, Khuller GK. ;Lectin-functionalized poly(lactide-co-glycolide) nanoparticles as oral/aerosolized antitubercular drug carriers for treatment of tuberculosis. Antimicrob Chemother 2004;54:761–6.
40) UpadhyayShivam, Parikh Ankit, Joshi Pratik, Upadhay U M and Chotai N P, Intranasal drug delivery system- A glimpse to become maestro; JAPS 01 (03): 2011; 34-44.
41) Ziyi Wen,Zhiqiang Yan, Kaili Hu, Zhiqing Pang, Xufei Cheng, Liang RanGuo, Quzhi Zhang, Xinguo Jiang, Liang Fang, Ren LaiOdorranalectin-conjugated nanoparticles: Preparation brain delivery and

pharmacodynamic study on Parkinson's disease following intranasal administration ,Journal of Controlled Release (2011).
42) MiLan Kanga, Hu-Lin Jiang, Sang Gyun Kanga, Ding DingGuoc,Deog Yong Lee a, Chong-Su Choc,Han Sang Yoo,Pluronic(R) F127 enhances the effect as an adjuvant of chitosan microspheres in the intranasal delivery of Bordetellabronchiseptica antigens containing dermonecrotoxin ,Vaccine 25 (2007) 4602-4610.
43) Parag M.Ved, Kwonho Kim, Poly(ethyleneoxide/propyleneoxide) copolymer thermoreversible gelling system for the enhancement of intranasal zidovudine delivery to the brain, International Journal of Pharmaceutics(2011).
44) Paun J.S.,Bagada A.A.,Raval M.K.,Nasal Drug Delivery –As An Effective Tool For Brain Targeting-A Review, International Journal Of Pharmaceutical And Applied Sciences/1(2)/2010.
45) Lianli Li, Nandi Indranil, Kim Kwon H.,Development of an ethyl laurate-based microemulsion for rapid –onset intranasal delivery of Diazepam, International Journal of Pharmaceutics 237 (2002) 77-85.
46) Huanga Juan, Garmiseb Robert J., Crowderc Timothy M., Mara Kevin, Hwanga C.Robin, Hickery b Anthony J., Miksztaa John A., Sullivana Vincent J., A novel dry powder influenza vaccine and intranasal delivery technology: induction of systemic and mucosal immune responses in rats, Vaccine 23(2004) 794-801.
47) Balazs DA,Godbey W.Liposomes for use in gene delivery. J.Drug Deliv 2011; 378(1-2): 326-497.
48) Pardridge WM.Preparation of Trojan Horse Liposomes (THLs) for gene transfer across the blood-brain barrier.Cold Spring HarbProtoc 2010; 4: pdb.prot 5407.
49) Kozlowska,H.,Jablonka,J.,Janowski,M., Kossut, M.,Doman'ska-Janik,K., Transplantation of an ovel human cord blood –derived neural-like stemcell line in aratmodel of corticalinfarct. StemCells Dev 16, 2007,481-488.
50) Sinden,J.D., Patel,S.N.,Hodges,H., Neural transplantation: Problems and prospects for therapeutic application.Curr.Opin.Neurol.Neurosurg.5, 1992, 902-908.
51) Li, J.Y.,Christophersen,N.S.,Hall,V., Soulet,D., Brundn, P.,Critical issues of clinical human embryonic stem cell therapy for brain repair.TrendsNerosci 31,2008,146-153.
52) Lusine Danielyana,RichardScha ferb, Andreasvon Amenln-ayerhoferc, Marine Buadzea, JuliaGeislera, Tim Klopfera, Ute Burkhardta, Barbara Prokscha, Stephan Varleysdonkd, Miriam Ayturanb, Gayane H. Buniatiana, Christoph H. Gleitera, William H.Freyll, Intranasal delivery of cells to the brain, European Journal of Cell Biology 88(2009)315-324.
53) Dollery,C., Therapeutic Drugs, second ed.Churchill Living stone, London Newyork, Toronto,1999, pp.M132- M136.
54) Harrington, R.A., Hamilton, C.W.,Brogden,R.N., Linkewich, J.A.Romankiewicz, J.A.,Heeel, R.C., Metoclopramide: an updated review of its pharmacological properties and clinical use ,Drugs 25,1983,451-494.
55) Zaki N.M.,Awad G.A.S.,, Mortada N.D., AbdElHady S.S.,Rapid–onset intranasal delivery of metoclopramide hydrochloride Part I .Influence of formulation variables on drug absorbtion in anesthetized ras; International Journal of Pharmaceutics 327(2006) 89-96.
56) Thorne, R.G., Lagalwar S.,Rahman, Y.E. and Frey II, W.H. Intranasal administration of insulin like growth factor-1(IGF-1) : a noninvasive CNS drug delivery strategy for by passing the blood-brain barrier,Growth Horm.IGF Res., 9(1999) 387.
57) Xin-FengLiua, John R.Fawecetta, Robert G. Thornea, Willliam H.Frey II, Non-invasive intranasal insulin-like growth factor-I reduces infarct volume and improves neurologic function in rats following middle cerebral artery occlusion, Neuroscience Letters 308 (2001) 91-94.
58) M.Bliss ,The history of insulin ,Diabetes Care 16(Suppl. 3) 1993, 4-7.
59) Eppstein D.A.,Longenecker J.P.,Alternative delivery systems for peptides and proteins as drugs, Crit.Rev.Ther.systemic medications,in : Y.W.Chien (Ed), Transnasal Drug Carrier Syst.5(1988) 99-139.
60) Lee V.H.L., Yamamoto A., Penetration and enzymic barriers to peptide and protein absorption, Adv.Drug.Deliv.Rev.4.(1990) 171-207.
61) Smith P.L.,Wall D.A,.Gochoco H., Wilson G.,Routes of delivery case studies.(5) Oral absorption of peptides and proteins, Adv.Drug.Deliv.Rev.8(1992) 253-290.
62) Davis S.S.,Developing delivry systems for peptides and proteins , Scrip Mag.May (1992) 34-38.
63) Kennedy F.P.,Recent developments in insulin deliver techniques ,Drugs 42(1991) 213-227.
64) Pickup J.C.,An introduction to the problems of insulin delivery, in : J.C. Pickup (Ed) , Biotechnology of Insulin Therapy, Blackwell Scientific, Oxford, 1991,pp.1-23.

65) Pontiroli A.E., Calderara A., Pozza G., Intranasal drug delivery potential advantages and limitations from a pharmacokinetic perspective, Clin.Pharm. 17(1989) 209-307.
66) Illum L., Davis S.S., Intranasal insulin: Clinical pharmacokinetics, Clin.Pharm. 23(1992) 30-41.
67) Banga A.K., Chien Y.W., Systemic delivery of therapeuticpeptides and proteins, Int. J. Pharm. 48 (1988) 15–50.
68) Chien Y.W., Chang Y., Historical developments of transnasal systemic medications, in: Y.W. Chien (Ed.), Transnasal Systemic Medications: Fundamentals, Developmental Concepts and Biomedical Assessments, Elsevier, Amsterdam, Adv. Drug Deliv. Rev. 4 1985, pp. 1–100.
69) Longenecker J.P., Nazlin – transnasal systemic delivery of insulin, in: Davis S.S., Illum L., Tomlinson E. (Eds.),Delivery Systems for Peptide Drugs, Plenum, New York,1986, pp. 211–220.
70) Pereswetoff-Morath L., Edman P., Dextran Microsphere as a potential drug delivery system for insulin – in vitro and in vivo properties, Int. J. Pharm. 124 (1995)37-44.
71) Aspden T.J., An evaluation of the potential use of chitosans in nasal peptide absorption systems, PhD Thesis, University of Nottingham, UK, 1996.

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