WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 6, 418-431. Review Article ISSN 2277– 7105

NOSE TO BRAIN DELIVERY AND DIFFERENT STRATEGIES FOR CNS DRUG DELIVERY

Tripathi Sapna*, Mukhopadhyay Sayantan and Kothiyal Preeti

Division of Pharmaceutical Sciences SGRRITS, Patelnagar Dehradun 248001.

Article Received on
12 April 2016,

Revised on 03 May 2016,
Accepted on 24 May 2016

DOI: 10.20959/wjpr20166-6126

***Corresponding Author**
Tripathi Sapna
Division of Pharmaceutical Sciences SGRRITS, Patelnagar Dehradun 248001.

ABSTRACT

Nose is an invasive route for delivery of drug to the CNS. For the delivery of drug to the CNS the major challenge is to crossing of BBB. So researches develops many strategies by which drug can be directly goes to CNS for treating many CNS diseases. Nasal delivery is one of them. In the nasal delivery lipophilic drugs are well absorbed and directly goes through the olfactory region to cerebrospinal fluid in the brain. When the other route are not allowed for low molecular weight drugs then nasal route is preferred. Nasal route is used because it protect from first pass metabolism, the surface area of nose is large, good penetration, rapid absorption, avoidance of harsh environment etc. Nasal route offers lower risk of overdose of CNS acting drugs because in this delivery drug dose is less than the other delivery. Many nasally applied dosage forms are available in market. Two third are locally acting decongestants and one third comprises a number of antimigraine drugs, peptide hormone analogs and nicotine nasal spray, all with the systemic effects. Now intranasal administration of drug delivery to brain especially for the treatment of CNS drug such as depression, epilepsy, angina pectoris, migraine etc.

KEYWORDS: BBB, Intranasal, different strategies, Marketed formulation of Nose delivery.

INTRODUCTION

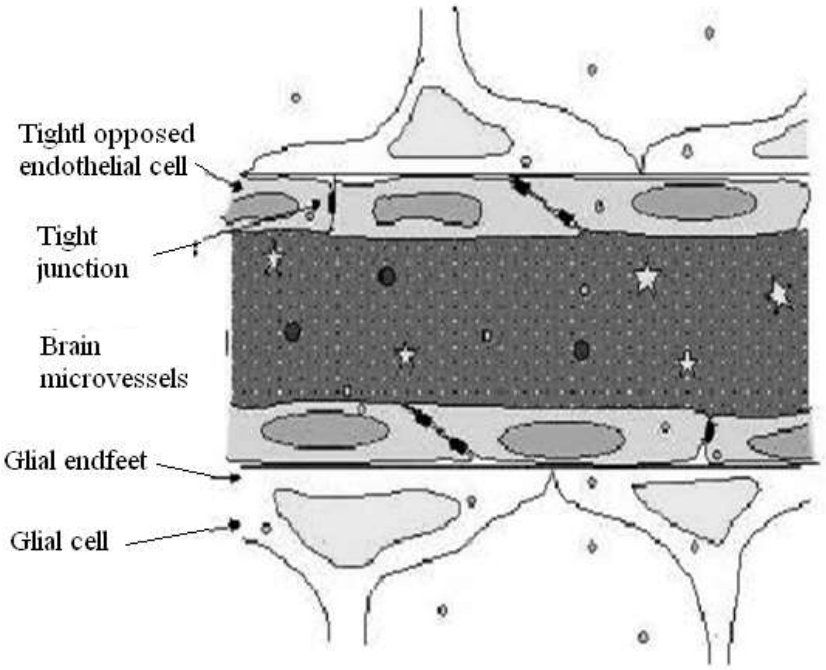
Brain is the most important organ of human body which is protected by the two layers which are blood brain barrier and blood cerebrospinal fluid barrier.For treating brain diseases crossing of BBB is a major challenge.BBB is a protective layer of brain which protect from the toxic substances present in the blood stream.For the treatment of many CNS disorders such as brain and spinal cord injury, brain cancer, Alzheimer, Parkinson's, Dipression, multiple sclerosis etc many noval delivery systems are developed.[1] Most of the drugs are

effective at their site of action but in the case of CNS drugs proper quantity of drug is not able to reach the brain by which they are discarded in the phase of the development for the clinical use.[2] blood brain barrier and cerebrospinal fluid barrier are two barrier which are responsible for the failure in the delivery of drug to the brain. In the delivery of CNS drugs it must be important that drugs should passes the BBB.[3] Nasal delivery of drug is the best way for direct drug delivery in the biophase of CNS active compounds because nasal delivery is able to bypass the BBB. It is also used for the administration of vaccines.[4,5] mostly for the systemic action of drug transmucosal route is used. Nasal drug delivery is an effective way for the topical therapies as well as systemic therapies because nasal cavity have low enzymetic environment, high permeability and high vasculature.so nose is suitable for delivery of drug molecules.[6,7] In the ayurvedic system of Indian medicines the nasal therapy is known as Nasaya karma.[8] Nasal application is a nonparenteral delivery system by which rapid onset of action is possible. By the nasal route only low molecular weight hydrophobic drugs are highly absorbed.[9] When the small molecular weight polar drugs, proteins and peptides are not administered by other route then nasal route is preferred.[10]

Problems associated with brain delivery

Blood Brain Barrier- Blood brain barrier was first recognized by the Lewandowsky in 1900 while he studying about the limited permeation of potassium ferro cyanate into the brain.[11] Blood Brain Barrier is a highly dense protective layer only allow the passage of selective molecule into the brain.[12] BBB is divided into two components which are Endothelial or capillary barrier and the Ependymal barrier.BBB is formed by a complex cellular system which consist endothelial cells, astroglia, pericytes, perivascular macrophages and basal lamina.[13] Brain is highly restricted by BBB. The cardiac output in human brain receives about 20%. BBB segregates brains from the circulating blood.[14] In the brain targeting, permeability through the BBB is a major problem.[15] Blood capillaries which are present in CNS are different in their structure from the other tissues blood capillaries. These structural difference in blood capillaries are responsible for permeability barrier within extracellular fluid in brain tissue and in blood within brain capillaries. Capillaries of vertebrate brain and spinal cord allow rapid movement of solute within the organs, with a special layer of endothelial cells are tightly sealed in these capillaries.[14] the surface area of BBB is grater than blood cereberospinal fluid barrier approximately 5000folds.[15] BBB is act as a rate limiting factor for the permeation of CNS drugs into the brain.BBB is only permeable for the transportation of nutrients such as blood glucose, proteins, peptides and peptide drugs.[16]

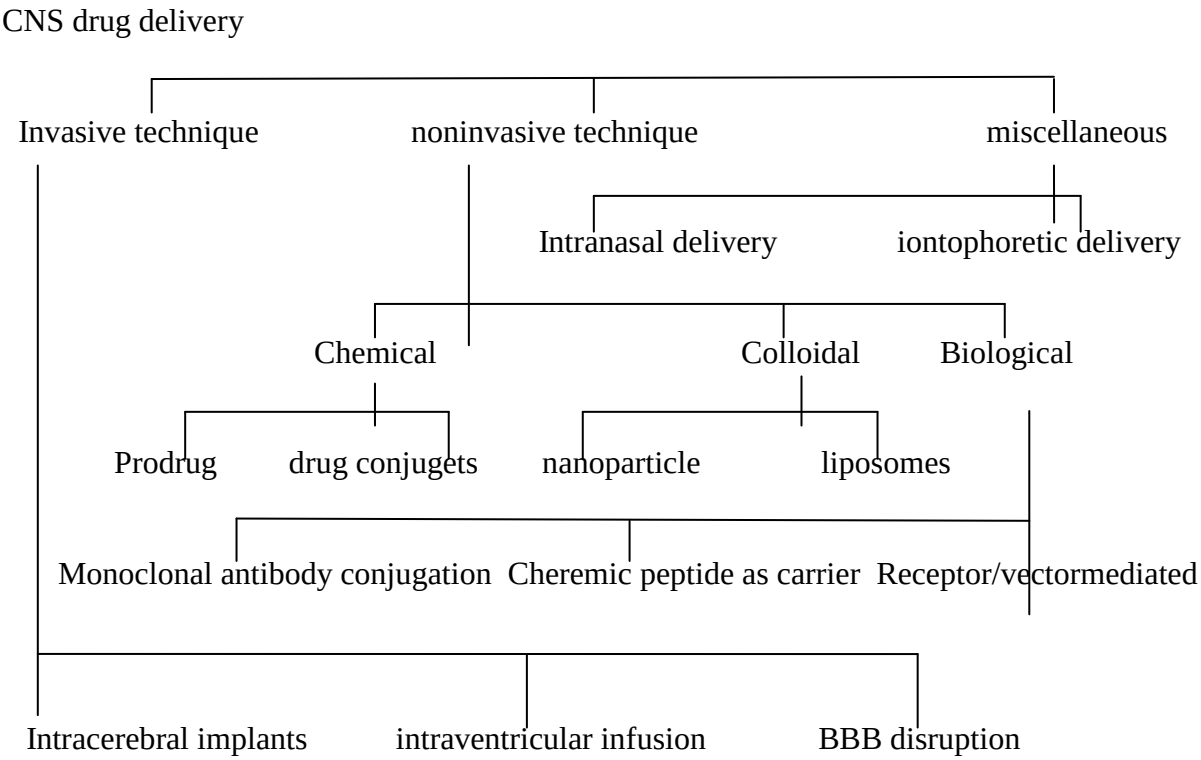
practically it is shown that if drugs are lipid soluble and used in brain's disorders can easily cross BBB by oral administration.[17]



The pericytes embedded in basal lamina in claw-like appendices by twisted together or inertwine the capillaries. Pericytes have their important functional properties such as- they intervene in a dispute in order to bring the inflammatory processes, regulation for the activity of endothelial cells of brain and for associate rapidly they include capillary like structure.[18,19]

Small lipophilic molecules are easily diffused by BBB is a common misconception because some small lipophilic molecules are not penetrate the brain, this is due to the presence of some active transport in BBB. Several ATP-binding cassette(ABC) are present in BBB.[20] these ABC transporters are responsible to expel out the multiplicity of drugs from the CNS. On the surface of BBB some natural transport system are also present which helps in the transport of some special large polar compounds into the brain. So these are also work as same as pseudotransporters, by carrier-mediated transcytosis transport small molecules and by receptor mediated transcytosis transport large molecules.[20,21]

Strategies to overcome the problems associated with CNS drug delivery-



Schematic representation of strategies to overcome the CNS drug delivery approach

Intracerebral implants

Now a days direct brain injections are used for crossing the BBB.[22] these injections are injected intrathecally or intraventricularly into CSF or either into brain parenchyma. This strategy used for implants containing drugs as a slow release depot into brain.[22,23] when the administration of drug is into the subarachnoid space then this is called intrathecal drug administration, while when injection or infusion given into lateral ventricle of brain that is called intraventricular administration.[24] major drawback of this approach is need of unique equipment and need of neurosurgery. If implanted directly into brain then this requires surgical involvement.[22] for the purpose of intracerebral implants neurosecretory cells are mainly used.[25]

Intraventricular infusion

By using intraventricular drug infusion, drugs are not properly delivered to brain parenchyma but they could easily distributed to the surface of the brain.[25] drugs by using ommaya reservoir can be infused intraventricularly. Subcutaneously a plastic reservoir implanted in the scalp and connected to the ventricles within the brain via an outlet catheter. Drug solution delivered to the ventricles by manual compression of reservoir by scalp and injected subcutaneously into implanted reservoir.[26]

Disrupting BBB

This technique is widely used for the CNS drug delivery.BBB may disrupt by the exposure to X-radiation and infusion of solvents(dimethyl sulfoxide, ethanol).[27] BBB permeability are different with effect of alcoholic and hypoglycaemic coma. The energy metabolism processes are responsible for the effects.[28]

Important techniques used in the disruption of BBB are-

a-Osmotic BBB disruption

when the osmotic agents administered peripherally they causes the opening of BBB.[23] when osmotic pressure generated it results transient opening of the barrier due to the variety of cyto-skeletal alterations.[22] by this barriers open quickly and remains open for 30 min. If drug is administered when barrier are open through same cannula then drug can freely enter into the CNS.[23]

b-Ultrasound induced disruption

Recently it has been studied that ultrasound is able to increase transport of hydrophobic drugs by BBB and target small volume within the tissue.[29]

Prodrug

By the help of prodrug formation the brain uptake of drugs can be improved. Basically prodrug are pharmacologically inactive compounds. They can be activated by chemical modification. Physicochemical properties such as membrane permeability and water solubility are improved by chemical change .by the administration of prodrug it is brought closer to receptor site and maintained there for longer period of time by the improved characteristic. Here prodrug converted into its active form. In the CNS active compounds these are released and show their therapeutic activity by the hydrolysis of modifying group.[30] drug's pharmacokinetic properties can be improved by using their prodrug form.[31] in prodrug, drugs covalently linked with an inert chemical moiety.[32]

Nanoparticles

Nanoparticles are 1-1000nm(µm) in size. These are solid colloidal carrier particles.[33] nanoparticles consist a macromolecular material in which active principle is dissolved, entrapped or encapsulated.[34] from the wall of the brain blood vessels nanoparticles are absorbed without transport of particles across the endothelium.

Liposomes

Liposome are small vesicles which can be produced by phospholipids and cholesterol. Liposomes are lipid vesicles which are nontoxic, biocompatible and biodegradable. Properties of liposome vary with the lipid composition, method of preparation, size and surface charge.liposomes are able to carrying hydrophilic, hydrophobic and amphoteric molecules. Liposomes are used as a carrier for drugs, enzymes,[35-38] proteins[39,40] and other macromolecules.[41,42] anticancer chemotherapy which is based on liposomes gives of reduced systemic toxicity and combined to selective drug delivery into tumor.[43]

Artinin/cheremic peptide as a carrier

it is used to deliver peptide to brain.[44,45] when a receptor specific monoclonal antibody or a cationized albumin are conjugated with therapeutic active compound it forms a cheremic antibodies are absorbed. Cationic antibodies produces minimum immunogenicity and fewer side effects in body.[46]

Intranasal delivery

Now a days for drug delivery to the brain, nasal route is mostly used through olfactory pathway.[47] nose provide a direct route to the brain.[48] intranasal delivery of protein is a newly non-invasive method which is harmless and successful method for targeting proteins into the CNS. It avoided the BBB and reduces systemic exposure.[49] by increasing the lipophilicity of transported molecules, entrance to CNS by nasal route can be improved.[22,23]

Advantage of nasal route-[50-52]

- Hepatic first pass metabolism is avoided.
- Easy in self administration
- This is an alternate to parenteral route
- It is non invasive
- Comfortable route
- Ease of administration
- Rapidly absorbed
- Fast onset of action
- Improve patient compliance
- Lower dose reduces side effects

Disadvantages-[52-55]

- Frequent administration of drugs can lead to mucosal damage
- Some drugs may causes irritation in nasal mucosa
- Rapid muco cilliary clearance
- Provide smaller absorption surface area when compared to GIT
- Changes of immunologic reactions
- Extract mechanism is not known
- The amount of drug reaches to different regions of brain and spinal cord are varies.

Nose anatomy and physiology

There are mainly two function of nose first is sense of smell and the second is filtration, heating and humidification of the inhaled. interior of nose refers to the nasal cavity.

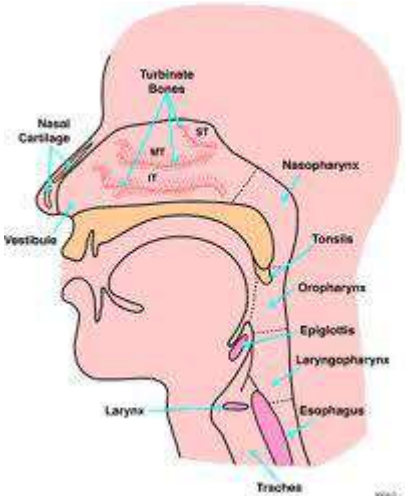
The human nasal cavity divided into two subcavity by septum.[56] the total volume of nasal cavity is about 16 to 19ml and surface area is about 180cm^2. Volume of each subcavity is approximately 7.5ml and surface area is 75cm^2.

Nasal cavity constituted by three parts

Vestibules

Respiratory region

Olfactory region



Vestibule

Nasal vestibule is an anterior part of nasal cavity. Its area is about 0.6cm^2.[57] when nostril open nasal vestibule dialated. Stratified squamous epithelium and keratinized epithelium with sebaceous glands covered the nasal portion.[57]

Respiratory region

Nasal respiratory mucosa is an important section which helps in delivering drugs systemically. It is also known as conchae and this is the largest part of nasal cavity. It is devided into three turbinates which are superior, middle and inferior turbinates. Nasal respiratory region is useful for delivering drugs systemically. It is constituted by epithelium, basement membrane and lamina propria. Nasal respiratory epithelium consist pseudostratified columnar epithelial cells, globet cells, basal cells and mucous and serous gland.[58]

Olfactory region

Olfactory region located on the roof of nasal cavity. As the respiratory region olfactory region is also pseudostratified but for the small perception it contains specialized olfactory receptor cells. Neuroepithelium of olfactory region is only a part of CNS which is exposed directly to the external environment.[59,60]

Suitable formulations/ dosage form for nose to brain delivery

Formulation/dosage form	Drug used	Mode of action
Powdered dosage form-		
1-Insufflators Ex-Trimel, Optinose	Ketamine, Amphetamine	It is used to deliver the drug substance for inhalation; it can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also.
2-dry powder inhaler	Zolmitriptan.	dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route or intranasal route.
3-dry powder inhaler devices capsule based		Easy to use design developed with emerging human, factors standards in mind.In this device Powder emptying can be confirmed through capsule window which remains open during inhalation.
4-dry powder inhaler devices		It was developed specifically for high dose, acute and chronic treatments .A very simple inhaler, suitable for emergency treatments or in situations where minimal usage instructions or medical supervision are available .It is low cost and is disposable
5-nasal powder sprayers Ex-Fit-lizer		In this chamber is compressed by hand, compressed air passes and

Unidose DP Solu vent		powder is emitted.
Liquid dosage forms-		
1-solutions and sprays		drug solutions are nasally administered as nasal drops, sprays, and as metered dose nebulizer. dose of the active ingredient administered depends upon the volume of drug and the concentration of drug in the formulation
2-suspension		For nasal administration suspension are prepared by suspending the micronized drug in a liquid diluent or carrier suitable for application to the nasal mucosa. The formulation of suspension form enhanced the insulin uptake and reduces blood glucose as compared with solution form.
Semisolid dosage forms-		
1-gels	Oxytocin,Metoclopramide Hydrochloride.	consisting of two or more components, one of which is a liquid, present in substantial quantity. with suitable rheological properties increase the contact time with the mucosa at the site of absorption
Devices		
1-insillation and rhinyl catheter		Catheters are used to deliver the drops to a specified region of nasal cavity conveniently
2-squeezed bottles		Squeezed nasal bottles are mainly used as delivery de-vice for decongestants. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside
3-metered dose pump sprays	oxytocin	The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are on the market.

4-mucosal atomizer device		Device designed to allow emergency personnel to delivery nasal medications as an atomized spray.
Liposomes	Tacrine hydrochloride	phospholipid vesicles composed by bilayer enclosingone or more aqueous compartments, in this drug can be entrapped or adsorbed.
Microsphers	Insulin , Desmopressin	Enhance absorption, sustained release, and also protects drug from enzymatic degradation.

Recent advances in nose to brain drug delivery

Iontophoretic delivery

According to a new research iontophoresis can be used for drug delivery in CNS. We can say that iontophoresis is an active introduction of ionised drugs into the tissues with the help of electric current. By the help of iontophoresis or phonophoresis biologically active agents can be delivered directly to the CNS by the olfactory pathway.[61]

Molecular Trojan Horses

Trojan horses are generally known as the endogenous ligands of specific BBB receptors.these receptors have the capacity to shuttle down the drugs inti the brain. In the regulation of the cerebral blood flow the vasoactive intestinal polypeptides are participated. So the invivo studies shows that with the low transport of peptide into brain their is no neuropharmacological effect produced which is attributable to the presence of BBB.

REFERENCES

1. Bummer PM. Physical chemical considerations of lipid based oral drug delivery-solid lipid nanoparticles, Critical Review; Therapeutic Drug Carrier System 2004; 21(2): 1-20, http://dx.doi.org//10.1615/CritRevTherDrugCarrierSyst,v21.i1.10
2. Begley DJ. Delivery of therapeutic agents to the central nervous system: the problems and the possibilities. Pharmacology and Therapeutics. 2004; 104: 29-45.
3. Shah SP, Misra A, Ganesh S and Shahiwala A. Drug delivery system to central nervous system: a review. J Pharm Pharmaceut Sci. 2003: 6(2): 252-273.
4. CIllum L. Nasal drug delivery: new developments and strategies. Drug Discov Today. 2002; 7: 1184- 1189.

5. Graff L.C., Pollock G.M. Nasal drug administration: potential for targeted central nervous system delivery. J Pharm Sci. 2005; 94: 1187-1195.
6. Uttarwar S, Formulation and development of *in situ* gelling system for nasal administration for an antie-metic drug ondansetron hydrochloride by using pluron-ics F127 and pluronics F68, Published by International Journal of Research in Pharmaceutical and Biomedical Sciences, Vol. 3 (3) Jul Sep2012,1103-1105.
7. Byeongmoon, J and Anna G, Lessons from Nature: Stimuli-Responsive Polymers and Their Biomedical Applications, Trends in Biotechnology, Vol. 20, July, 2002; 305-311.
8. Hicke A.J., Pharmaceutical Inhalation Aerosol Technology, 2nd ed Marcel Dekker, Inc: NewYork, 2004. Pagar Swati Appasaheb et al.: A Review on Intranasal Drug Delivery System 344.
9. Osth, K; Paulsson, M; Bjork, G and Edsman, K, "Evaluation of drug release from gels on pig nasal mucosa in a horizontal using chamber", ***J Control Rel.***, 2002; 83: 377-388.
10. 1Wadell,, C; Bjork, E and Camber, O, "Nasal drug deliver-evaluation of an *in vitro* model using porcine nasal mucosa", ***Eur J Pharm Sci.***, 1999; 7: 197-206.
11. Begley DJ. Delivery of therapeutic agents to the central nervous system: the problems and the possibilities, Pharmaceutical Therapeutics 2004; 104(1): 29-45.http//dx.doi.org/10.1016/j.pharmthera.2004.08.001.
12. Zur Muhlen A,Mehnert W.Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles . Pharmagine 1998; 53: 552.
13. Jawahar N, Gowthamarajan K, Meyyanathan SN,SoodiS,lirenic H.Brain delivery by solid lipid nanoparticles for CNS drugs, International Journal of pharmaceutics Research and development 2001; 3(4): 206-216.
14. Ambikanandan Misra, Ganesh S., Aliasgar Shahiwala, Shrenik P. Shah, Drug delivery to the central nervous system: a review, J Pharm Pharmaceut Sci, 2003; 6(2): 252-273.
15. Shadab A. Pathan, Zeenat Iqbal, Syed M. A. Zaidi, Sushma Talegaonkar, Divya Vohra, et. al., CNS Drug Delivery Systems: Novel Approaches, Recent Patents on Drug Delivery & Formulation, Bentham Science Publishers Ltd, 2009; 3: 71- 89.
16. Egleton RD, Davis TP. Development of neuropeptide drugs that cross the blood–brain barrier. NeuroRx 2005; 2(1): 44-53.
17. Ambikanandan Misra, Ganesh S., Aliasgar Shahiwala, Shrenik P. Shah, Drug delivery to the central nervous system: a review, J Pharm Pharmaceut Sci, 2003; 6(2): 252-273.
18. J. Bernacki, A. Dobrowolska, K. Nierwinska, A. Malecki. Physiology and pharmacological role of the blood-brain barrier, Pharmacol.Rep., 2008; 60: 600-622.

19. J.A. Kim, N.D. Tran, Z. Li, F. Yang, W. Zhou, M.J. Fisher. Brain endothelial hemostasis regulation by pericytes, J.Cereb.Blood Flow Metab. 2006; 26: 209-217.
20. Begley, D.J. Delivery of therapeutic agents to the central nervous system: the problems and the possibilities. Pharmacol. Ther. 2004; 104: 29–45.
21. Pardridge, W.M. Molecular Trojan horses for blood–brain barrier drug delivery. Curr. Opin. Pharmacol. 2006; 6: 494–500.
22. Chopra D, Gulati M, Saluja V, Pathak P, Bansal P. Brain permeable nanoparticles. Recent Pat CNS Drug Discov. 2008; 3: 216-225.
23. Mcdannold N, Vykhodtseva N, Hynynen K. Blood-brain barrier disruption induced by focused ultrasound and circulating preformed microbubbles appears to be characterized by the mechanical index. Ultrasound Med Biol. 2008; 34: 834-840.
24. Kabanov AV, Batrakova EV. New Technologies for Drug Delivery across the Blood Brain Barrier. Curr Pharm Des. 2004; 10: 1355–1363.
25. Vyas SP, Khar RK. Targeted and controlled drug delivery novel carrier systems. 1st ed. CBS Publishers and distributors; 2007; 487-509.
26. Noe B, Hagen buch B, Stieger B, and Meier P J Isolation of a multi specific organic anion and cardiac glycoside transporter from rat brain. ProcNatlAcadSci USA 1997; 94: 10346–10350.
27. Mayordomo F, Renau-Piqueras J, Megias L, Guerri C, Iborra FJ, Azorin I. Cytochemical and stereological analysis of rat cortical astrocytes during development in primary culture: Effect of prenatal exposure to ethanol. Int J Dev Biol 1992; 36: 311–21.
28. Yorulmaz H, Seker FB, Oztas B. The effects of hypoglycemic and alcoholic coma on the blood-brain barrier permeability. Bosn J Basic Med Sci. 2011; 11: 108-112.
29. Ka-Yun NG, Cho CW, Henthorn TK, Tanguay RL. Effect of heat preconditioning on the uptake and permeability ofr123 in brain microvessel Endothelial cells during mild heat treatment. J Pharm Sci. 2004; 93: 896-907.
30. Schwarz JB, et al. Novel cyclopropyl β-amino acid analogues of pregabalin and gabapentin that target the α2-δ protein. J. Med. Chem 2005; 48: 3026-3035.
31. Bormann J. Electrophysiology of GABAA and GABAB receptor subtypes. Trends Neurosci 1988; 11: 112–116.
32. Jeanneret LJ. The targeted delivery of cancer drugs across the blood-brain barrier: chemical modifications of drugs or drug-nanoparticles? Drug Discov Today. 2008; 13: 1099-1106.

33. Witt KA, Davis TP. CNS drug delivery: Opioid peptides and the blood-brain barrier. The AAPS Journal. 2006; 8: E76- E88.
34. Panyam J, et al. Polymer degradation and in vitro release of a model protein from poly (d,l- lactide-co-glycolide) nano and microparticles. J. Control. Release 2003; 92: 173-187.
35. Gregoriadis G. Drug entrapment in liposomes. FEBS Lett 1973; 36: 292-296.
36. Arun Rasheed1, I Theja1, G Silparani1, Y Lavanya1, CK. Ashok Kumar. CNS Targeted Drug Delivery: Current Perspectives, JITPS 2010; 1(1): 9-18.
37. Silverman RB, Andruszkiewicz R, Nanavati SM, Taylor CP, Vartanian MG. 3-Alkyl-4-aminobutyric acids: the first class of anticonvulsant agents that activates L-glutamic acid decarboxylase. J. Med. Chem 1991; 34: 2295-2298.
38. Fellner S, et al. Transport of paclitaxel (Taxol) across the blood-brain barrier in vitro and in vivo. J. Clin. Invest 2002; 110: 1309-1318.
39. Van de Waterbeemd H, Smith DA, Beaumont K, Walker DK. Property-based design: optimization of drug absorption and pharmacokinetics. J. Med. Chem 2001; 44: 1313-1333.
40. Kerns EH. High throughput physicochemical profiling for drug discovery. J.Pharm. Sci 2001; 90: 1838-1858.
41. Kakee A, Terasaki T, Sugiyama Y. Brain efflux index as a novel method of analyzing efflux transport at the bloodbrain barrier. J. Pharmacol. Exp. Ther 1996; 277: 1550-1559.
42. Jaehde U, Langemeijer MWE, De Boer AG, Breimer DD. Cerebrospinal fluid transport and disposition of the quinolones ciprofloxacin and pefloxacin in rats. J. Pharmacol. Exp. Ther 1992; 263: 1140- 1146.
43. Somogyi G, Nishitani S, Nomi D, Buchwald, Prokai L, Bodor N. Targeted drug delivery to the brain via phosphonate derivatives: Design, synthesis and evaluation of an anionic chemical delivery system for testosterone. Int. J. Pharm 1998; 166: 15-26.
44. Chen P, Bodor N, Wu WM, Prokai L. Strategies to target kyotorphin analogues to the brain. J. Med. Chem 1998; 41: 3773-3781.
45. Pardridge WM. CNS drug design based on principles of blood-brain barrier transport. J Neurochem. 1998; 70: 1781–1792.
46. Bickel U, Yoshikawa T, Landaw EM, Faull K F, Pardridge WM. Pharmacologic effects in vivo in brain by vectormediated peptide drug delivery. Proc Natl Acad Sci. 1993; 90: 2618–2622.
47. Vyas SP, Khar RK. Targeted and controlled drug delivery novel carrier systems. 1st ed. CBS Publishers and distributors; 2007; 487-509.

48. Mathison S, Nagilla R, Kompella UB. Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? J Drug target. 1998; 5: 415-441.
49. Wolf CD. Nosy neuroprotection: intranasal administration of neuroprotective agents to the brain.Cryonics Magazine. 2011; 28: 18-20.
50. Malerba F, Paoletti F, Capsoni S, Cattaneo A. Intranasal delivery of therapeutic proteins for neurological diseases. Expert Opin Drug Deliv. 2011; 8: 1277-1296.
51. Lee VHL. Enzymatic barriers to peptide and protein absorption, CRC Crit. Rev. Ther. Drug Carrier Syst. 1988; 5: 69–97.
52. Ohwaki K, Ando H, Watanabe S, Miyake Y, Effects of dose, pH and osmolarity on nasal absorption of se-cretin in rats. J Pharm Sci. 1985; 74: 550-2.
53. Arora P, Sharma S, Garg S. Permeability issues in nasal drug deliv- ery. Drug Discov Today. 2002; 7(18): 967-975.
54. Inagaki M, Sakakura Y, Itoh H, Ukai K, Miyoshi Y. Ma-cromolecu-larpermeability of the tight junction of human nasal mucosa. Rhinology 1985; 23: 213-221.
55. Satish BB, adhikrao VY, Amelia MA, Rajkumar M. Bio availability of intranasal drug delivery system, Asian J of Pharmaceutics 2008; 201-15.
56. Gizurarson S and BechgaardE. Intranasal administration of insulin to humans. Diabetes Res Clin Prac 1991; 12: 71-84.
57. Swatantra K. S. Khushwaha, et al. Advances in nasal trans-mucosal drug delivery. J app pharm sci, 2011; 1: 21-28.
58. Illum L. Nasal drug delivery: possibilities, problems and solutions. J Control Release, 2003; 87: 187-198.
59. Graff L.C., Pollock G.M. Nasal drug administration: potential for targeted central nervous system delivery. J Pharm Sci. 2005; 94: 1187-1195.
60. Merkus F.W., Verhoef J.C., Schipper N.G., Marttin E. Nasal mucociliary clearance as a factor in nasal drug delivery. Adv Drug Deliv Rev. 1998; 29: 13-38.
61. Charlton S., Jones N.S., Davis S.S., Illum L. Distribution and clearance of bioadhesive formulations from the olfactory region in man: Effect of polymer type and nasal delivery device. Eur J Pharm Sci. 2007; 30: 295- 302.
62. C. Rousselle, P. Clair, J. M. Lefauconnier, M. Kaczorek, J. M. Scherrmann, J. Temsamani, Mol. Pharmacol. 2000; 57: 679.