AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A REVIEW : NANOPARTICLES AS SPECIFIED CARRIERS IN TARGETED BRAIN DRUG DELIVERY SYSTEM

R.Sunitha[1*], D.Harika[1], A. Phani kumar[2], K. Suria Prabha[1], P. Muthu Prasanna[1]

1. Hindu college of Pharmacy, Amaravathi road, Guntur.

2. Alliance institute of advanced Pharmaceuticals and health sciences, Hyderabad.

ABSTRACT

The worldwide CNS pathology incidence displayed that about 1.5 billion people suffer from CNS disorders. The worrying fact that , delivering drugs to the CNS is impaired by the presence of the blood-brain barrier (BBB) that represents the main obstacle for CNS drug development, many hydrophilic drugs and neuropeptides etc are may have difficulty in crossing the blood-brain barrier. It is important to consider not only the net delivery of the agent to the CNS, but also the ability of the agent to access the relevant target site within the CNS. Many strategies have been developed to deliver the drug into brain by crossing the BBB are chemical delivery systems, magnetic drug targeting, or drug carrier systems such as antibodies, liposomes or Nanoparticles. Among those, Nanoparticles have got a great concentration as the potential targeted drug delivery systems in the brain recently. Nanoparticles (NP) are solid colloidal particles ranging in size from one to 1000nm that may be utilized as brain drug delivery carriers. Coating of Nanoparticles with drug molecules are as carriers to cross the BBB and transport the drugs to the specific sites in brain where they are needed. NPs may provide slow drug release in blood and thereby reduces the peripheral toxicity.

Key words: BBB, Drug delivery to brain, Nanotechnology, Colloidal drug carriers.

*Corresponding Author Email: raminenisunitha@gmail.com,

Received 16 August 2011, Accepted 23 August 2011

Please cite this article in press as: Sunitha R *et al.*, A Review :Nanoparticles As Specified Carriers In Targeted Brain Drug Delivery System. American Journal of PharmTech Research 2011.

INTRODUCTION

Drugs may be administered directly into the CNS or administered systematically (e.g., by intravenous injection) for targeted action in the CNS. Here the blood-brain barrier (BBB) represents an intractable obstruction for a large number of drugs, including antibiotics, antineoplastic agents, and a variety of central nervous system (CNS)-active drugs, especially neuropeptides. Generally 98% of all small-molecule drugs do not cross the BBB, and nearly 100% of large-molecule drugs do not cross the BBB. Various strategies have been developed with improved pharmacodynamic effects to treat brain disorders. Drug delivery to the brain requires advances in both, drug delivery technologies and drug discovery[1]. Drugs that are effective against diseases in the CNS and reach the brain via the blood compartment must pass the BBB usually by nanoparticles drug delivery system which is an advanced technology to deliver drug molecules into the brain. The main advantage of Nanoparticles technology is that they masquerade the blood-brain barrier restrictive features of the therapeutic drug molecule.

These polymeric nanoparticles (NP) have been proposed as fascinating colloidal systems that allow slow drug release in brain and the improvement of therapeutic efficacy and reduction of toxicity of large variety of drugs. Due to their targeting ability they are very advantageous than other conventional drug delivery systems. Once the NP reaches the desired tissue, release of the drug may occur by desorption, diffusion through the NP matrix or polymer wall or NP erosion, or combination of any or all mechanisms[2]. Some examples of drugs which are taken up with nanoparticles are, adsorption of drugs to polysorbate 80-coated nanoparticles has been shown to increase the transport of a number of substances across the BBB including the polar hexapeptide dalargin, tubocurarine and the lipid-soluble P-glycoprotein substrates loperamide and doxorubicin. It has been reported that poly (butylcyanoacrylate) nanoparticles is able to deliver hexapeptide dalargin, doxorubicin and other agents into the brain which is significantly obstructed by BBB.

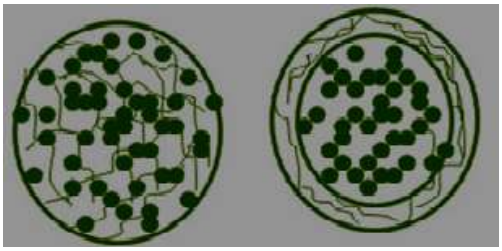
These systems are attractive because the methods of preparation are generally simple and easy to scale-up. Due to their small size, nanoparticles penetrate into even small capillaries and are taken up within cells, allowing an efficient drug accumulation at the targeted sites in the body. The use of biodegradable materials for nanoparticles preparation, allows sustained drug release at the targeted site over a period of days or even weeks after injection [3].

NANOPARTICLES FOR TARGETING DRUG DELIVERY:

The nanoparticles are the solid colloidal particulate systems with size ranging from 1 to 1000nm that are utilized as drug delivery system[2].

- Polymeric nanoparticles are used as potential drug delivery systems due to its target ability to particular organ or tissue.
- Certain properties like hydrophobicity, lipophilicity, surface charge needs to be altered, so uptake of nanoparticles into cells increased. This can be done by manipulating the use of polymers[4].
- Nanoparticles generally made up of biocompatible and biodegradable polymers which are obtained from either natural or synthetic source.
- The kinetics of drug release from nanoparticles depends on strength of hydrophobic and lipophilic interactions between the polymer and drug and polymer degradation rate.
- Based on arrangement of drug and polymer matrix Nanoparticles are classified into two types[5]:

1. **Nanospheres**: drugs are either absorbed or entrapped inside the polymer matrix.
2. **Nanocapsules**: drug present in the inner liquid core, and external surface of nano particles are covered by the polymeric membrane.



(A) (B)

Figure 1: Schematic diagram of Nanosphere (A), and Nanocapsule (B) [6].

Advantages of Nanoparticles [6,7,8,9]:

1) Targeting ability of drugs to particular organ or tissue.
2) Increase in bioavailability.
3) Development of new formulation, which are safer.
4) Ability to sustained release of drugs.
5) High carrier capacity.
6) Prolonged circulation time.
7) Stable in blood.

8) Acquiescent to small molecules, peptides, proteins, or nucleic acids.

Disadvantages:

1) Increase in cost of formulation, due to high manufacturing costs.
2) May cause allergic reactions.
3) Over use of polyvinyl alcohol as a stabilizer may have toxic reactions.

Characterization of nanoparticles:

Characterization of nanoparticles can be done by using a variety of different techniques, after synthesizing nanoparticles. Here various manufacturing methods have been included for synthesis of nanoparticles, they are Emulsion polymerization, Interfacial polymerization, Desolvation evaporation, Solvent deposition.

Common techniques for characterization of nanoparticles are [2,6]:

- Electron microscopy (TEM, SEM),
- Atomic force microscopy (AFM),
- Dynamic light scattering (DLS),
- X-ray photoelectron spectroscopy (XPS),
- Powder X-ray diffraction (XRD),
- Fourier transform infrared spectroscopy (FTIR),
- Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF),
- Ultraviolet-visible spectroscopy,
- Dual polarization interferometry,
- Nuclear magnetic resonance (NMR).

BRAIN TARGETTED DRUG DELIVERY:

Rate-limiting role of the BBB in brain drug development:-

To demonstrate the difficulty of the exertion that have to be overcome for brain targeting, a brief intercellular description of the blood–brain barrier (BBB) is furthermore incorporated[1,10,11].

- The major challenge to CNS drug delivery is the blood-brain barrier (BBB), which limits the access of drugs to the brain substance.
- Human brain is constrained and detached from circulatory network by a highly efficient blood brain barrier.

- BBB is constituted by relatively impervious endothelial cells with rigid junctions, enzymatic activity and active efflux transport systems.

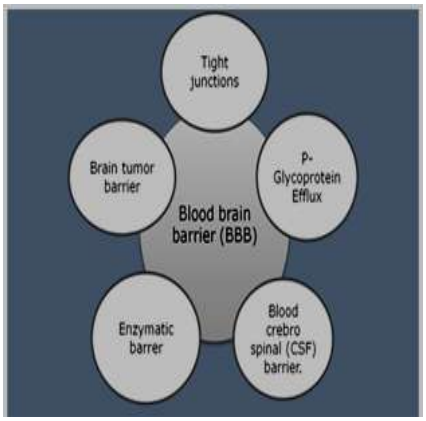


Figure 2 Constitution of BBB

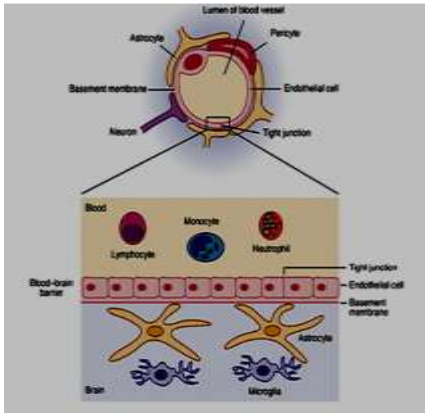


Figure 3 Cross section of a cerebral capillary of BBB (copied from expert reviews in molecular medicine@2003 cambridge university press, http://www.expertreviews.org)

- Physiologically, blood-brain barrier is designed in such a manner that it can only permit the transport of molecules essential for functional activity of brain.
- It efficiently prevents flow of water-soluble molecules from blood circulation into central nervous system, and can also decrease concentration of lipid-soluble molecules.
- Advances in understanding of the cell biology of the BBB have opened new avenues and possibilities for improved drug delivery to the CNS.
- Several carrier or transport systems, enzymes, and receptors that control the penetration of molecules have been identified in the BBB endothelium.
- Receptor-mediated transcytosis can transport peptides and proteins across the BBB.
- Methods are available to assess the BBB permeability of drugs at the discovery stage to avoid development of drugs that fail to reach their target site of action in the CNS.
- Various strategies that have been used for manipulating the blood-brain barrier for drug delivery to the brain include osmotic and chemical opening of the blood-brain barrier as well as the use of transport/carrier systems.
- Other strategies for drug delivery to the brain involve by passing the BBB.
- Various pharmacological agents have been used to open the BBB and direct invasive methods can introduce therapeutic agents into the brain substance.

Transfer mechanism across BBB[1, 12]

- The transport of solutes and drugs in to the brain is regulated by transport system present at the BBB.

- The transport system expressed at BBB may mediates either influx of solutes or drugs form blood to brain or the active efflux of solutes or drugs from brain to blood

There are four transfer mechanisms by brain for transport of nutrients and essential nutrients.

- 1.Diffusion(Passive and active diffusion)
- 2. Facilitated
- 3.Active transport
- 4.Transcytosis

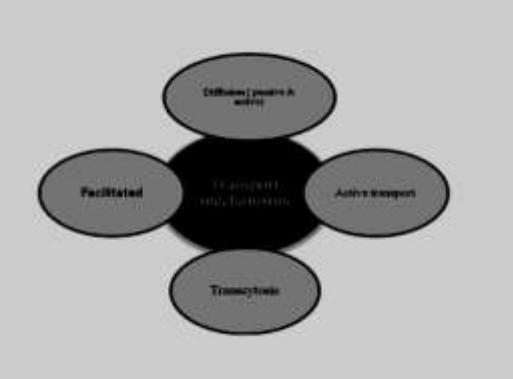


Figure 3: Transfer mechanism across BBB

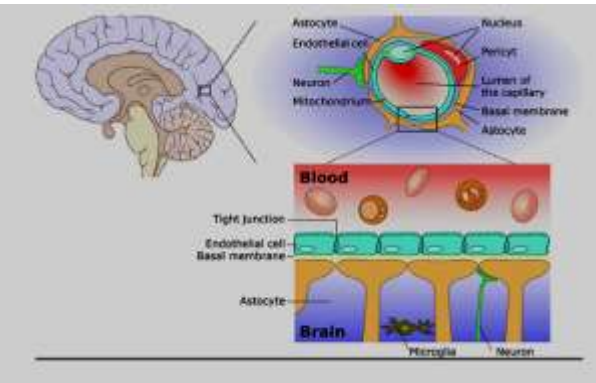


Figure4: Schematic representation of brain and composition of BBB

Brain Targeting Technology[11]:-

- The usual non invasive approach to solve the brain drug delivery problem is to lapidate the drug.
- The water-soluble parts of the drug restrict BBB transport.
- Conversion of water-soluble drug into lipid-soluble prodrug is the predictable solution to the BBB problem.
- It is important to consider not only the net delivery of the agent to the CNS, but also the ability of the agent to access the relevant target site within the CNS.
- Various routes of administration as well as conjugations of drugs, e.g., with liposomes and nanoparticles, are considered.
- Some routes of direct administration to the brain are non-invasive such as transnasal route whereas others involve entry into the CNS by devices and needles such as in case of intrathecal and intra cerebroventricular delivery.
- Systemic therapy by oral and parenteral routes is considered along with sustained and controlled release to optimize the CNS action of drugs[13].

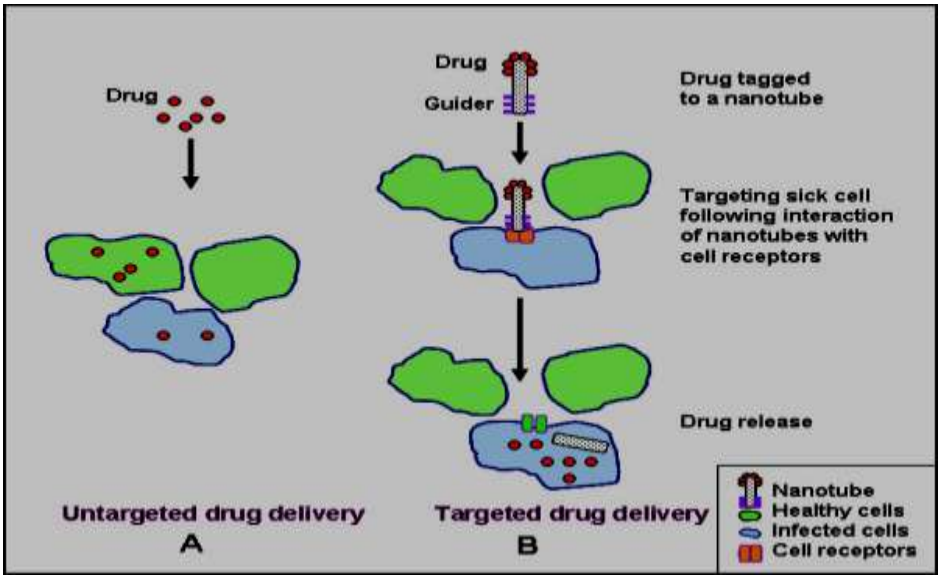


Figure 6: Drug targeting technology [14]

Possible systems for drug delivery to brain:

There are, various approaches have been proposed to improve the delivery of similar drugs to this tissue, in which one of the important approach is colloidal drug carriers, (Colloidal drug carrier systems such as macular solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10 to 400 nm diameter) and nanotechnology. This article mainly discuss about the nanotechnology in brain targeting drug delivery[11].

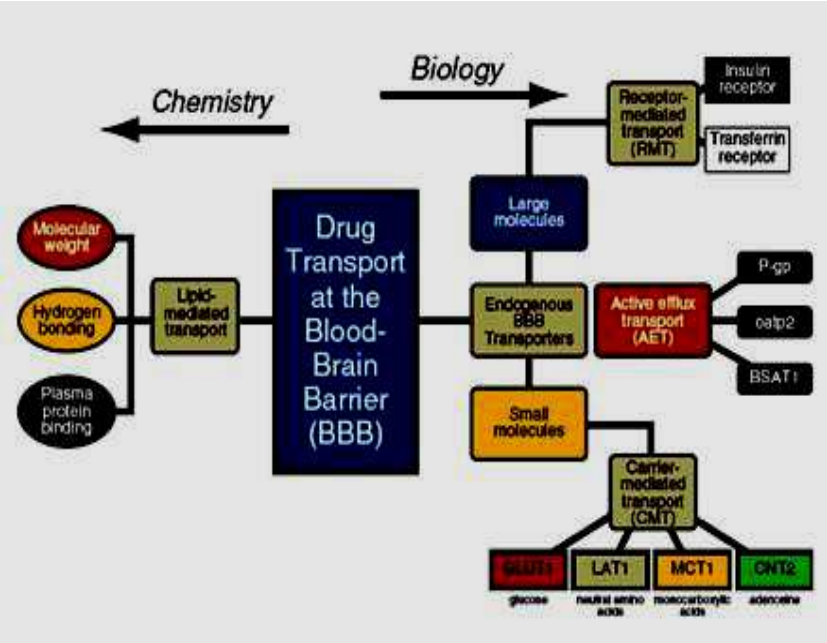


Figure 7: Outline of a blood-brain barrier drug targeting program - chemistry-based and biology-based approaches for developing BBB drug-targeting strategies[11]

NANOTECHNOLOGY:

- Nanotechnology is proved to be more competent for enhancing drug delivery to brain.
- The nanoparticles are the drug carrier system which is made from a broad number of materials such as: poly(alkylcyanoacrylates), polyacetates, polysaccharides, and copolymers.
- In some cases it is reported to mimic molecules that would normally be transported to brain. For example, polysorbate-coated nanoparticles are thought to mimic low-density lipoprotein (LDL), allowing them to be transported across the capillary wall and into the brain.

Mechanisms of Nanoparticle Transport across the BBB:

- The mechanism by which the nanoparticles transported in to the brain is not fully understood. There are six different possibilities exists that could enable enhanced transport of drug across the blood brain barrier (Dehouck *et al.*, 1997).
- Adhesion of nanoparticles to brain blood vessel walls: Troster *et al.*, (Troster *et al.*, 1990) suggested that adhesion of nanoparticles to the inner surface of the brain blood vessels resulting in higher radioactivity levels with polysorbate 80 coated 14C label nanoparticles.
- Fluidization of endothelium by surfactants: The possibility that enhanced drug transport is due to the surface activity of polysorbate 80 and resulting fluidization of the endothelium. Experiment with such surfactants using tail flick test and dalargin as experimental drug showed that polysorbate 20, 40 and 60 were also able to transport dalargin to brain and produced an antinoceptive effect (Kreuter 2004)**.**
- Opening of tight junctions of endothelium: Another possible explanation of enhanced transport of drug across BBB is opening of endothelial lining of the brain blood vessels. Hyper osmotic pressures may open these junctions for instance, enhancing drug transport in to the brain (Kreuter *et al*., 2000).
- Transcytosis across the brain endothelial cells: After uptake of nanoparticles by endothelial cells, the nanoparticles and adsorbed drug may be delivered to the brain cells by transcytosis. Evidence that low density lipoproteins (LDL) particles may be transported across the BBB by receptor mediated transcytosis (Dehouck *et al*., 1997).
- Blockage of the glycoprotein in the brain endothelial cells: One of the possibilities for enhancement of brain transport with nanoparticles could be the inactivation of p-

glycoprotein efflux pump. This glycoprotein is present in the brain endothelial (Cordon-Cardo *et al*., 1989)**.** This is responsible for multidrug resistance which represents a major obstacle to cancer chemotherapy .Surfactants including polysorbate 80 were shown to inhibit the efflux system and to reverse multidrug resistance (Woodcock *et al*., 1990)**.**

- Endocytosis by the brain vessel endothelial cells: This is the most likely mechanism for brain transport of drug uptake by endothelial cells lining the brain blood vessels. These cells are similar to reticuloendothelial cells which are able to endocytose particulate matter under certain circumstances. After endocytosis, delivery of drug occurs with or without nanoparticle degradation and the drug would enter the residual brain by diffusion(Kreuter 2000).

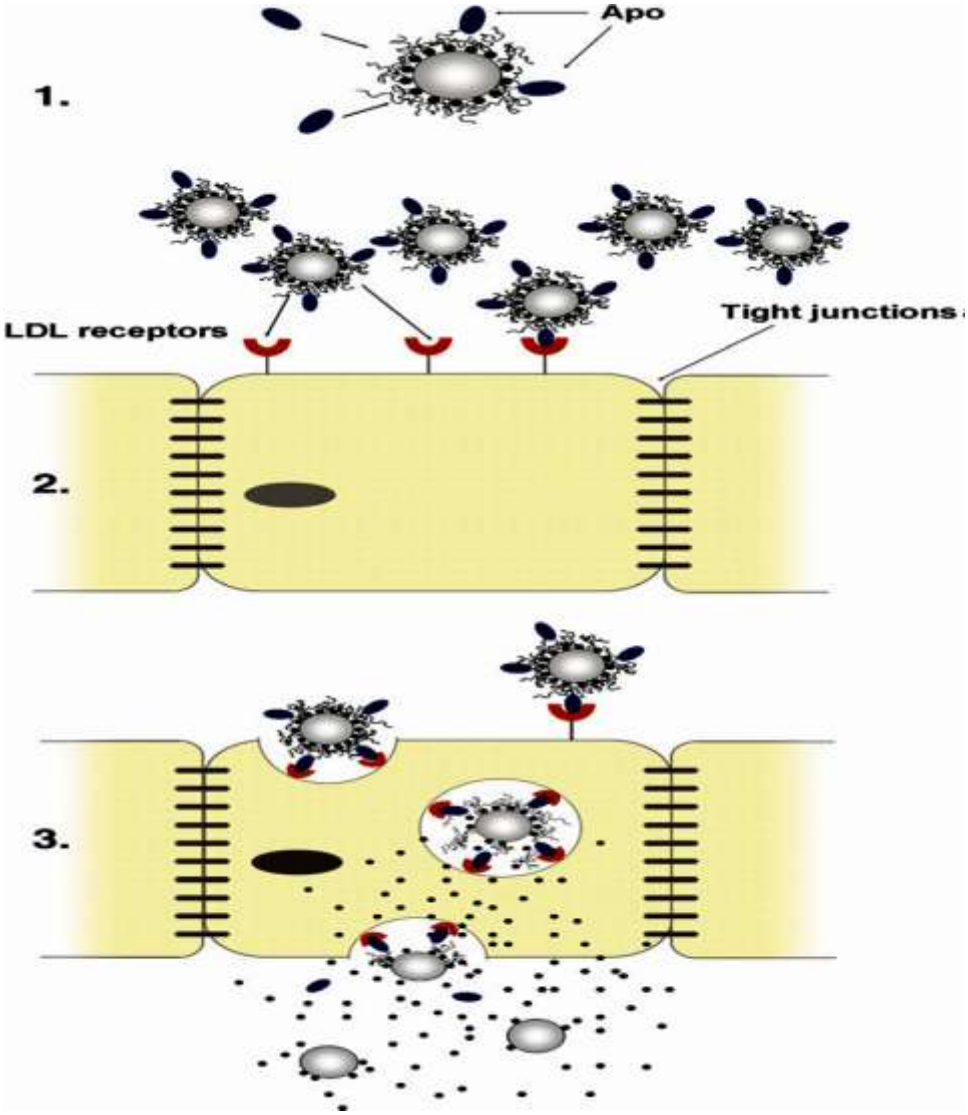


Figure 8: Mechanism of nanoparticles through endocytosis process[10]

Nanoparticulate systems for brain targeted delivery of drugs:-

- Nanoparticles are polymeric particles made of natural or artificial polymers ranging in size between about 10 and 1000 nm (1 mm).
- They were initially devised as carriers for vaccines and anticancer drugs. Simultaneously the use of nano particles for ophthalmic and oral delivery was investigated (Bachhav *et al.*, 2007).
- Due to their small size, nanoparticles can penetrate small capillaries and are taken up by the cells which allows for efficient drug accumulation at the target sites in the body
- The drugs or other molecules may be dissolved into the nanoparticles, entrapped, encapsulated or adsorbed or attached.
- Nanoparticles were found to be helpful for the treatment of the distributed and very destructive brain tumors.
- Nanoparticles provide enormous advantages relating to drug targeting, delivery and release and, with their supplementary prospective to combine diagnosis and therapy.
- The main goals are to develop their stability in the biological situation, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and contact with biological barriers.
- Nanoparticles and nano formulations have already been applied as drug delivery systems with great success;
- The first drug that was delivered to the brain using nanoparticles was the hexapeptide dalargin (Tyr-D-Ala- Gly- Phe-Leu-Arg), a Leu-enkephalin analogue with opioid activity[15].
- Another Study shows that PEGylated PHDCA (n-hexadecylcyanoacrylate) nanoparticles made by PEGyalated amphiphilic copolymer penetrate into the brain to a larger extent than all the other tested nanoparticles formulations, without inducing any variation of the BBB permeability.
- Valproic acid-loaded nanoparticles showed reduced toxic side effects of valporate therapy, not by reducing the therapeutically necessary dosage but by inhibition of formation of toxic metabolites[16].
- Drugs like dipeptide kytorphin, loperamide, tubocurarine, the NMDA receptor antagonist MRZ 2/576, doxorubicin, etc had been successfully transported into the brain by using nanoparticles as carriers[17].

- Targeting of Tacrine into the brain with polysorbate80-coated poly(n- butylcyanoacrylate) nanoparticles for treating the Alzheimer's disease[3].
- The result defines two important requirements to take into account in the design of adequate brain delivery systems, long-circulating properties of the carrier and appropriate surface characteristics to permit interactions with endothelial cells.

The types of nanoparticles used in nanotechnology includes;-

1) Coated nanoparticles
2) Solid Lipid nanoparticles (SLN)
3) Nanogels

Advantages of nanotechnology:-

1) Due to the small size of nanoparticles, they penetrate into even small capillaries and are taken up within cells, allowing an efficient drug accumulation at the targeted sites in the body.

2) The use of biodegradable materials for nanoparticles preparation, allows sustained drug release at the targeted site after injection over a period of days or even weeks.

Approaches:

- One of the recent advanced researches is introducing a drug called Photofrin along with iron oxide nanoparticles for targeting the brain tumors. Photofrin is a type of photodynamic therapy (PDT), in which the drug is drawn through the blood stream to tumors cells; a special type of laser light activates the drug to attack the tumor. Iron oxide is a contrast agent used to enhance magnetic resonance imaging (MRI) [18].
- Another advanced technique is introducing magnetized, iron-containing nanoparticles directly into the brain tumor. These nanoparticles, also known as "Trojan horses", are vigorously taken up by the tumor cells, because they are coated with a layer of sugar molecules. There by cancer cells covered by iron containing nanoparticles, which can then heated by electromagnetic field. This over heating causes the killing of the tumor cells.

Future aspects of brain targeting:

There are many technological challenges to be met, in developing the following techniques[6, 7, 20, 21, 22,]:

- Development of Nano - drug delivery systems, to deliver large amount of drugs to the specific areas in controlled release manner; "Controllable release profiles, especially for sensitive drugs"

- Materials which are suitable for nanoparticles those are biocompatible and biodegradable, because some sensitive drugs may prone to degradation.
- Nanoparticles to improve devices such as implantable devices or nanochips for nanoparticles release, or multi reservoir drug delivery-chips.
- The major problem with nanoparticles is the cytotoxicity of nanoparticles or their degradation products, so, improvements in biocompatibility are a main concern of future research.
- Nanoparticles for tissue engineering like the delivery of cytokines to control cellular growth and differentiation, and stimulate regeneration; or for coating implants with nanoparticles in biodegradable polymer layers for sustained release.
- Universal formulation schemes that can be used as intravenous, intramuscular or per oral drugs, at the same time multifunctional nanoparticles are also developed for various therapies.

CONCLUSION:-

Brain Targeting has got the attention of the many researchers due to its application in various diseases related to CNS. Only few drugs can penetrate the BBB and enters the CNS, so various systems are developed for delivering drug molecules to the brain. In those drug delivery systems, one of the best delivery system is use of nanoparticles. The result defines two important requirements to take into account in the design of adequate brain delivery systems, long-circulating properties of the carrier and appropriate surface characteristics to permit interactions with endothelial cells. This system has clinical benefits like reduced drug dose, decreased side effects, non invasive routes, and more patient compliance. Even though this delivery system has many advantages, we still require developing a cost effective system that can be used in various CNS disorders efficiently with minimum side effects. And however this technique is advantageous, some nanoparticles has also been repeatedly reported toxic reactions (for example, TiO2 nanoparticles could damage brain-cells).

REFERENCES:

1. Vyas SP, Khar RK. Targeted & Controlled Drug Delivery Novel Carrier Systems, CBS Publishers & Distributors, New Delhi, 2002.
2. Bala SH, Kumar MN. Plga nanoparticles in drug delivery: The state of the art. Crit Rev Ther Drug Carrier Syst 2004; 21(5):387-422.

3. Kumar MS, Santhi K. Targeted delivery of tacrine into brain with polysorbate80-coated poly (n-butylcynoacrylate) nanoparticles. Eur J Pharm Biopharm 2008; (70):75–84.
4. Kreuter J. Nanoparticles as drug delivery system, Encyclopedia of nanoscience and nanotechnology, H. S. Nalwa (Editor), American Scientific Publishers, Stevenson Ranch, Calif., 2004:161–180.
5. Nahar M, Dutta T, Murugesan S, Asthana A, Mishra D, Rajkumar V, Tare M, Saraf S, Jain NK. Functional polymeric nanoparticles: An efficient and promising tool for active delivery of bioactive. Crit Rev Ther Drug Carrier Syst 2006; 23(4):259-318.
6. Sai Hunuman sag. "NANOPARTICLES" pharmmainfo.net, 3-10-2010.
7. Kopecek J. Smart and genetically engineered biomaterials and drug delivery systems. Eur J Pharm Biopharm 2003; 20:1-16.
8. Torchilin VP. Structure and design of polymeric surfactant- based drug delivery systems, J Control Release. 2001; 73:137-72.
9. Muller-Goymann CC. Physicochemical characterization of colloidal drug delivery systems such as reverse micelles, vesicles, liquid crystals and nanoparticles for topical administration. Eur J Pharm Biopharm 2004; 58:343-56.
10. Blasi P *et al.*, Solid lipid nanoparticles for targeted brain drug delivery. www. science direct.com. Adv Drug Delivery Reviews 2007, 59, 454–477.
11. Shah S. An over view of brain targeted drug delivery system.Pharmainfo.net 2009: 1-6.
12. Lockman PR. Nanoparticle technology for drug delivery across the blood-brain barrier. Review in Drug development and industrial pharmacy 2002; 28 (1):1-12.
13. Packhaeuser CB, Schnieders J, Oster CG, Kissel T. In situ forming parenteral drug delivery systems: an overview. Eur J Pharm Biopharm 2004; 58:445-55.
14. Suri SS. Nanotechnology-based drug delivery systems http://www.occupmed.com /content/2/1/16.
15. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release 200; 70:1-20.
16. Patel B. Recent Trends in Brain Targeted Drug Delivery Systems: An Overview in pharmainfo.net, Latest Reviews 2007;5 (2).
17. Chakraborty C. Future prospects of nanoparticles on brain targeted drug delivery Published online: 2 December 2008.

18. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on chitosan-based micro- and nanoparticles in drug delivery. J Control Release 2004; 100:5-28.
19. Niculescu Duvaz I, Springer CJ. Antibody directed enzyme prodrug therapy (ADEPT): a review. Adv Drug Delivery Reviews 1997; 26:151-72.
20. Pardridge WM. Brain Drug Targeting: The Future of Brain Drug Development. Cambridge, England: Cambridge University Press; 2001:1-353.
21. Pardridge WM. BBB-genomics: creating new openings for brain-drug targeting. Drug Discovery Today.2001; 6:381-383.
22. Santinijr, JT, Richards AC, Scheidt R, Cima MJ, Langer R. Microchips as Controlled Drug-Delivery Devices. Angew. Chem. Int. Ed., 2000; 39:2396-407.
23. Haag R. Supramolecular Drug-Delivery Systems based on Polymeric Core-Shell Architectures. Angew Chem Int Ed 2004; 43:278-82.
24. Bae Y, Fukushima S, Harada A, Kataoka K. Design of Environment-Sensitive Supramolecular Assemblies for Intracellular Drug Delivery: Polymeric Micelles that are Responsive to Intracellular ph Change. Angew Chem Int Ed 2003; 42:4640-43.
25. Sood A, Panchagnula R. Parenteral Route: An Opportunity for Protein and Peptide Drug Delivery. Chemical Reviews 2000; 101:3275-303.
26. Pardridge WM. Drug and gene targeting to the brain via blood-brain barrier receptor-mediated transport systems. Int Congr Ser 2005 ;(49):49–62.
27. Olivier JC. Drug transport to brain with targeted nanoparticles. NeuroRx 2005; 2:108–119.
28. Olivier JC, Fenart L, Chauvet R, Pariat C, Cecchelli R, Couet W. Indirect evidence that drug brain targeting using polysorbate 80-coated polybutylcyanoacrylate nanoparticles is related to toxicity. Pharm Res 1999; 16:1836–1842.