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A Review on Brain Targeted Drug Delivery System

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ABSTRACT:
Brain is act as a central processing unit in human body as like a computer. This controls all the body systems under one organ. The brain is a delicate organ and nature has very efficiently protected it. The drug accessibility to the CNS in limited by the Blood brain barrier (BBB). Various brain disorders are Parkinson, Alzheimer, Meningitis, Brain abscess, Epilepsy, Multiple sclerosis, late – stage neurological trypanosomiasis (sleeping sickness). Drug delivery to the brain requires advances in drug delivery technologies, due to presence of the Blood brain barrier(BBB). Only small lipid soluble drug in the circulation are delivered to the brain cell. Therefore, practical strategies are required for mediating the drug transport across Blood brain barrier(BBB). In order to distribute the drugs in to the CNS via passing the Blood brain barrier (BBB), Drug carrier systems (Antibodies, Liposomeor Nanoparticles).

I. INTRODUCTION:

The brain is the most versatile and sophisticated organ in the body and is protected by a very effective barrier as Blood brain barrier (BBB) and Blood cerebrospinal fluid barrier(BCSFB). BBB is one such barrier which separates but not isolates brain from all other body components. The CNS is protected by BBB & BCSFB. This controls the entry of compounds in to the brain, there by regulating brain homeostasis.
In the CNS targeted action can be achieved by direct administration of the drugs in to the CNS.

(1) BBB can considerably impair the effect of the large number of drugs (Eg: Antibiotics, Anti neoplastic agents and neuropeptides-CNS stimulant drug). Because of it is obstinate hindrance affect.
(2) From some recent studies, it has been represented that the blood brain barrier (BBB) is usually. Does not cross by almost 100% of large molecule drugs and 98% of small molecules drugs.
(3) Drug discovery and drug delivery technologies are two main fields where Nanoparticle drug delivery system(NDDS) is one of the advanced technology that can be utilized to delivery drug molecules directly in to the brain.

Advantages

- Side effects and toxicity reduces.
- Dose of drug reduces by targeting organ.
- Avoids degradation of drug (1^{st} pass metabolism).
- Bioavailability increases.
- Permeability of proteins and peptides increases.

Disadvantages:

- Enhances decreases from target.
- Difficult to target tumor cells.
- Advanced technology requirement.
- Sometimes it may toxicity.
- Difficult to maintain stability of dosage form.

(Eg; Released erythrocytes have to be stored at 4*c).

BRAIN TARGETED DRUG DELIVERY SYSTEM:

The brain is important organ. It is protected with Blood brain barrier(BBB) and it is difficult to target it.

Blood Brain Barrier:

The BBB is a highly selective permeability barrier that separate the circulating blood from the brain extracellular fluid (BECF) in the CNS.

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The blood consists of a monolayer of polarized endothelialcells(EC) connected by complex tight junctions.
It is a continuous zipper like high junctioned endothelial cellular layer.
The structure of these tight junctions was first determined in the 1960's by TOM REES, MORRIES KROMOSKY and MILTONE BRITMAN.
Therefore, only lipid soluble solutes that can freely diffuse through the capillary endothelial membrane may passively cross the BBB.

Structure of BBB:

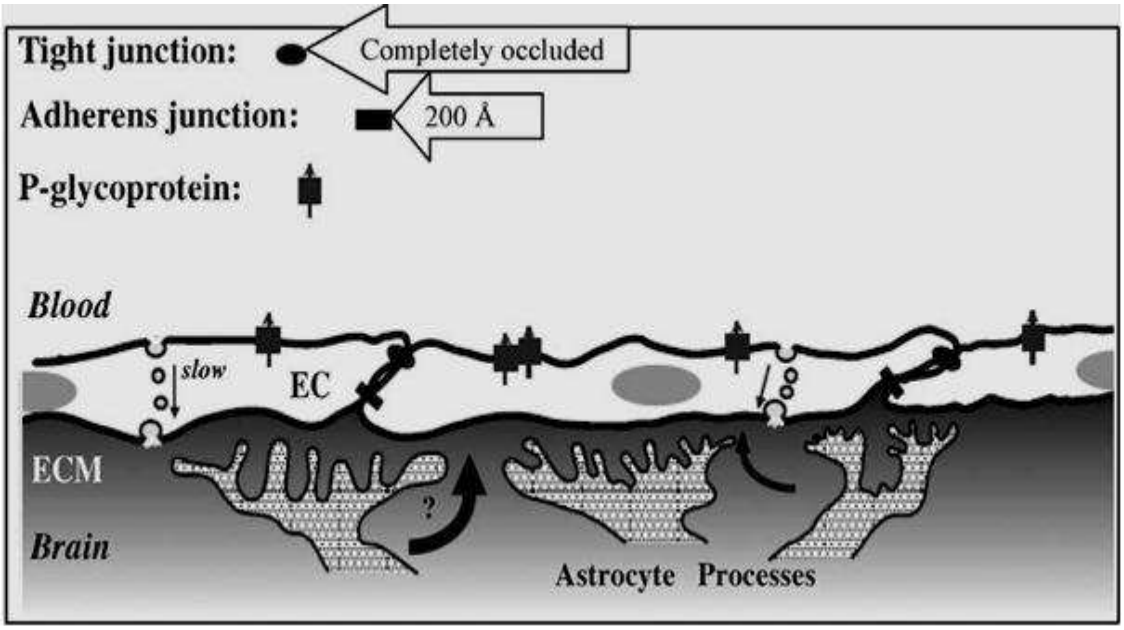

Figure 1: Anatomical structure of Blood Brain Barrier (BBB).

Functions of BLOOD BRAIN BARRIER:

- **T**he main function of Blood brain barrier is to protect the brain and keep it isolated from harmful toxins that are potentially in the Blood steam.
- The Blood brain barrier allows the passage of water, some gases, and lipid soluble molecules by passive diffusion
- The Blood brain barrier acts very effectively to protect the brain from many common or unwanted bacterial and infections.
- Blood brain barrier works as a dynamic biological entity, in which active metabolism and carrier mediated transports occur.
- The BBB limits both transcellular and paracellular passage of cells and molecules from the systemic circulation in to the CNS vice versa.

Drug Delivery to the Blood Brain Barrier:

Difficult for drugs to pass through the BBB. A study was conducted todeterminedthe factors that influence a compound's ability to transverse the BBB. In this study, they examined several different factors to investigate diffusion across BBB. The study found that barrier permittivity is"based on the measurement of the surface activity and as such takes into account the molecular properties of both hydrophobic and charged residues of the molecule of interest.

Problems faced in Drug delivery:

The first of these is that a lot of times, even if a compound transverse the barrier, it does not do it in a way that the drug is in a therapeutically relevant concentration. This can have many causes, the most simple being that the way the drug was produced only allows a small amount to pass through the barrier.

Another cause of this would be the binding to the proteins in the body rendering the drug ineffective to either be therapeutically active or able to pass through the barrier with the adhere proteins.

Another problem that must accounted for is the presence of enzymes in the brain tissue that could render the drug inactive.

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The drug may be able to pass through the membrane fine, but will be deconstructed once it is inside the brain tissue rendering it useless.

All of these problems that must be addressed and accounted for in trying to deliver effective drug solutions to the brain tissue.

Possible Solutions:

- ✓ Exosomes to deliver treatments across the BBB.
- ✓ Pro-drugs.
- ✓ Peptide masking.
- ✓ Receptor-mediated permeabilizers.
- ✓ Loaded microbubble –enhanced focused ultrasound.

DRUG TRGETING TO BRAIN IS A DIFFICULT PROCESS, WHY?

In this above portion of the article we are clearly understood that small molecules readily cross the BBB. Howeve, in fact, <2% of small molecules cross the BBB easily. In the comprehensive Medicinal Chemistry(CMC) data base there are > 7000 drugs established, and only 5% these drugs treat the CNS disorders. It has been investigated that 100% large molecules drugs and 98% of small molecule drugs do not cross BBB.

For a small molecule drug to cross BBB in significant amount, the molecule must have two important characteristics like molecular mass must be under 400 Da and high lipid solubility. Due to these reasons the brain drug targeting becomes more difficult for the pharmaceutical industries.

Types of Nano Particles For CNS Drug Delivery:

Solid lipid Nanoparticles:

Solid lipid Nanoparticles are colloidal particles composed of biocompatible or biodegradable lipid matrix that is solid at body temperature exhibit size range of 100-400 nm. Solid lipid Nanoparticles are a stable lipid based nanocarrier with a solid hydrophobic lipid core, in which the drug can be dissolved or dispersed. They are made with biocompatible lipids such as triglycerides, fatty acids and waxes. They are generally of small size allowing them to cross tight endothelial cell of BBB and escape from the reticuloendothelial System (RES). The term "lipid" has a boarder sense here and includes triglycerides (Eg: tristearin), fatty acid (Eg: stearic acid), partial glyceride (Eg: Imwitor), steroids (Eg: cholesterol), and waxes (Eg: acetyl palmitate). High-pressure homogenization or micro emulsification can be used for manufacturing of Nanoparticles. SLN are widely used for the delivery of active pharmaceutical ingredients to the brain.

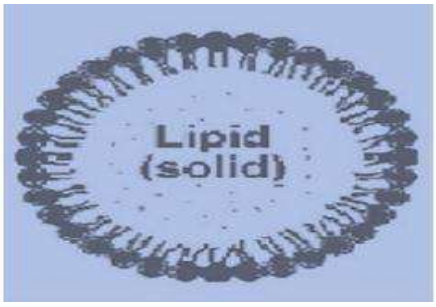

Fig2:Solid lipid Nanoparticles

A newer version of SLN called nanostructure lipid carrier(NLC), with increased drug loading are also become popular recently for brain targeting, which are composed of solid lipid and certain amount of liquid lipid, maintaining the solid state at both body and room temperature.

Lipid based Nano Particles:

-LIPOSOMES:

Liposomes, first described in 1965 are established drug and gene delivery carrier with clinical evidence of efficacy and several commercially available approved clinical formulations. Such as liposomes consists of bilayer phospholipid system in which watersoluble drugs could reside in the aqueous phase enveloped by the phospholipid bilayerand the lipophilic drugs, could directly integrate into the membrane. Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural nontoxic phospholipids. Due to their size and hydrophobic and hydrophilic character, liposomes are promising systems for drug delivery. Researchers are actively investigating on several advanced versions of liposomes such as long circulating (PEGylated) liposomes, triggered

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release liposomes, liposomes containing nucleic acid polymer, ligand targeted liposomes, and liposomes containing combination of drugs in order to achieve better drug delivery. Liposomes have been largely utilized for brain drug delivery, for the treatment of cerebral ischemia, for delivery of opioid peptides and brain tumors. Targeted brain delivery using liposomal systems resulted in considerable increase of drug concentration in Brain /in vitro cell lines.

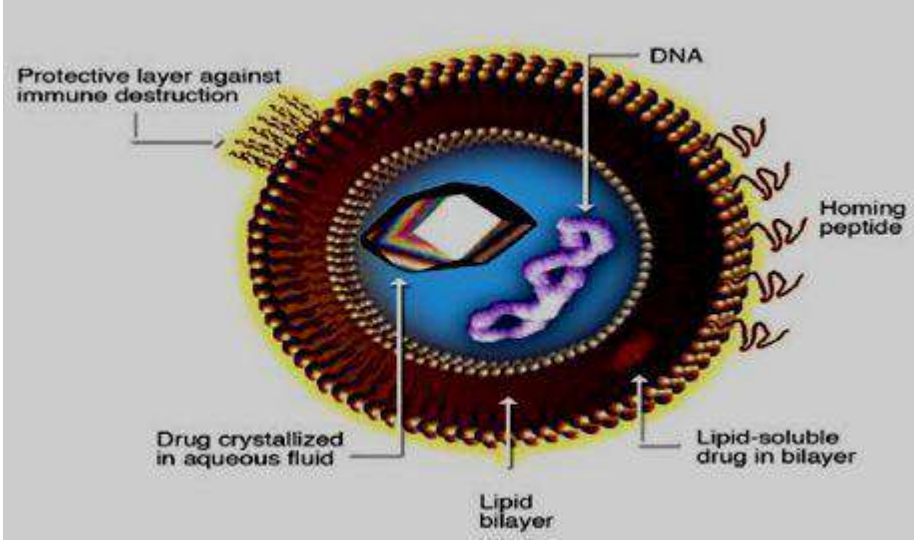

Fig3: Liposomes drug delivery.

CATIONIC LIPOSOMES:

Cationic liposomes containing positively charged lipids have been developed and initially used as transfection vehicles, to deliver genetic material (DNA) in to the cell, avoiding lysosomes digestion. One example of cationic liposomes uses bola amphiphiles, which contain hydrophilic group surrounding a hydrophobic chain to strengthen boundary of the Nano-vesicle containing the drug. Bola amphiphiles a no vesicles can cross BBB, and they allow controlled release of the drug to target sites.

Polymer based Nanoparticles:

POLYMERIC NANO-PARTICLES:

Nanoparticles are, colloidal particles, less than 1000 nm, that can be used for better drug delivery and prepared either by encapsulating the drug with in a vesicle and or by dispersing the drug molecule with in a matrix. Polymeric Nanoparticles are the nanosized carriers, made of natural or synthetic polymers, in which the drug can be loaded in the solid state or in solution, or absorbed or chemically linked to the surface. As a drug carrier, Nanoparticles have significant advantages like better availability, systemic stability, high drug loading, long blood circulating, and selective distribution in the organs /tissue for long half-life. They have outlined various mechanisms for Nanoparticles mediated drug uptake by the brain.

These includes,

(1) Enhanced retention in the brain blood capillaries, with an absorption on to the capillary walls, resulting in a high concentration gradient across the BBB.

(2) Opening of tight junction due to the presence of Nanoparticles.

(3) Transcytosis of Nanoparticles through the endothelium.

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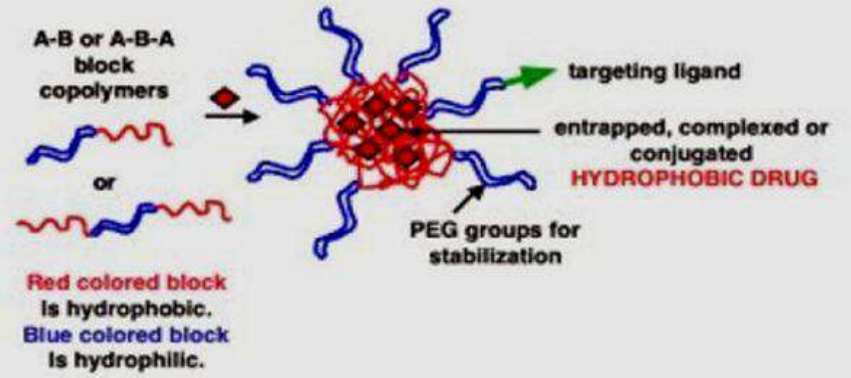

Fig4: Targeted polymeric micelles.

DENDRIMERS:

Dendrimers are a unique class of synthetic polymers which has a major role in Nano technological advances of drug delivery. The term "Dendra" in "Dendrimers" is derived from the GREEK which means tree and therefore appropriately describes its architecture. A typically symmetric around the core, and when suffiently extended it often adopts a spheroidal three-dimensional morphology in water. Novel Dendrimers based drug delivery systems consisting o G3 polyamidoamine (PAMAM) and surfactant conjugated dendritic nanocongugates have been successfully applied for targeted brain delivery. Some advantages of Dendrimers include their branching structure and the control of surface functionality, making them excellent carrier for more then one single drug to the brain; they have a high loading capacity and low toxicity. Limitations of their use include the high-cost manufacture and the need for assessment of long term human health consequence of Dendrimers exposure in Vivo.

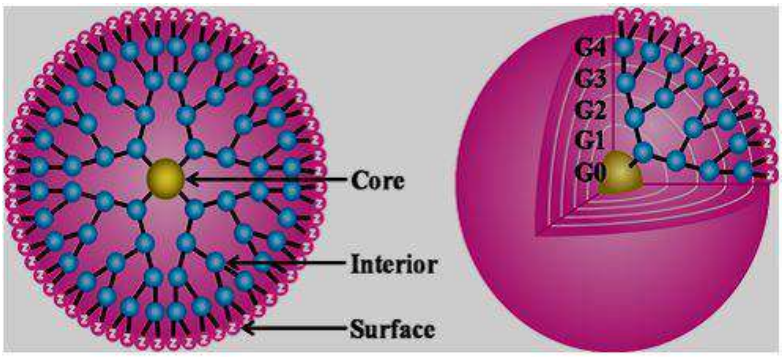

Fig5: Schematic presentation of Dendrimers as a Nano scaffold with a core.

FACTORES EFFECTING ON BRAIN TARGETING DRUG DELIVERY SYSTEM:

- Cerebral blood flow.
- Systemic enzymatic stability.
- Clearance rate of drug/polymer.
- Cellular enzymatic stability.
- Lipophilicity of the drug.
- Concentration gradient of the drug/polymer.
- Affinity of the efflux proteins (Eg: P-gp).
- Sequestration by other cells.
- Molecular weight of the drug.
- Metabolism by other tissue.

II. CONCLUSION:

Now a day, many young researchers are attracted toward brain targeting due to it's immense application in the treatment of various CNS diseases, because mostly drugs unable to cross the BBB. This review discusses one of the novel technology "nanotechnology" that has been developed to target the brain and passes various clinical benefits such as reduced drug dose, less side effects, noninvasive route, and better patient compliance. The treatment of brain diseases is particularly challenging because the delivery of drug. Molecules to the brain is often precluded by a variety of physiological, metabolic and Biochemical obstacles that collectively comprise

the BBB, BCB and BTB.Drug delivery directly to the braininterstitium has recently been markedly enhanced through the rational design of polymer-based drug delivery systems. In addition to enhanced brain transport, these systems also provide additional advantages as extended or controlled release of drugs and protection from degradation before reaching the targeted site leading to decreased dose or lesser frequency with decreased or no side effects.

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