"A Review on Different Techniques for Brain Targeting"

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ABSTRACT

Brain is act as a central processing unit in human body as like a in computers. This controls all the body systems under one organ. To reach a drug up to brain, its' a challenging task. In this review we added techniques that can easily cross the Blood Brain Barrier (BBB). Number of drugs unable to cross BBB easily, so that by using these techniques drug can easily reach to targeted sites. Techniques such as Pro drug, Liposome's, Nanotechnology, Microspheres, Polymeric Micelles and Micro emulsions and Dendrimers are helpful to transfer drug at brain targeted site. Figures in this article can easily explain the basic mechanism of preparation and its hypothetical views to understand the concept of targeted drug delivery system. This article will help on review of these techniques in short manner for students.

Keywords: *BBB- Blood Brain Barrier, CNS – Central Nervous System, TDDS – Targeted Drug Delivery System.*

INTRODUCTION[1-6]

Brain is an important organ in human body, which controls all body functions. Any disorders or disease related to brain are very difficult to control. Because it is coated by Blood Brain Barrier.(BBB). To provide a drug to brain is not possible with conventional drug delivery system. By using targeted drug delivery system we can easily cross BBB and reached drug up to brain. In this review we included some techniques that can enhance the availability of drug in barin.

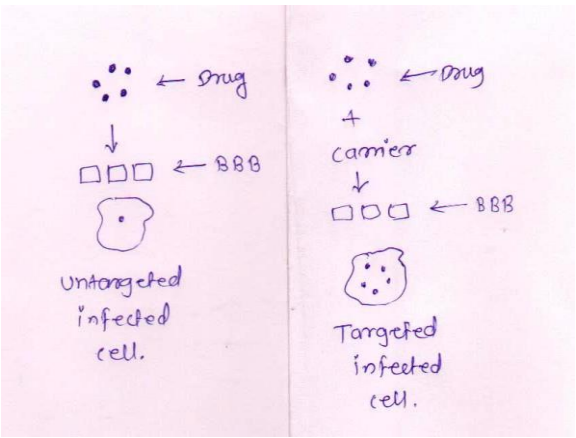

Fig. 1: Figure Showing Targeted Drug Delivery System

ADVANTAGES[4-6]

1. Side effect and toxicity reduces.
2. Dose of drug reduces by targeting organ.
3. Avoids degradation of drug (first pass metabolism).
4. Bioavailability increases.
5. Fluctuation in concentration decreases.
6. Permeability of proteins and peptide increases

DISADVANTAGES[4-6]

1. Enhances clearance from target.
2. Difficult to target tumor cells.
3. Advanced techniques requirements.
4. Skill persons required.
5. Sometimes it may causes toxicity.
6. Difficult to maintain stability of dosage form, e.g. Resealed erythrocytes have to be stored at 4^0c.

BRAIN TARGETED DRUG DELIVERY SYSTEM[6-9]

The brain is important organ, it is protected with Blood Brain Barrier and it is very difficult to target it, unless using modified drug delivery system. The blood–brain barrier is made up of endothelial cells, which are connected by tight junctions. The blood–brain barrier only receives the material like water, some gases, and lipid-soluble molecules by passive diffusion method, also the selective transport of molecules such as glucose and amino acids. Astrocytes are formed blood–brain barrier. To study BBB have provides new opportunities for increasing drug delivery to the CNS. Different techniques are used for targeting the blood brain barrier for drug delivery to the brain include carrier system, prodrug approach, liposomes, nanoparticles, dendrimers.

1. Blood-Brain Barrier (BBB)
2. Blood-Cerebrospinal Fluid Barrier (BCF)
3. Blood-Tumor Barrier

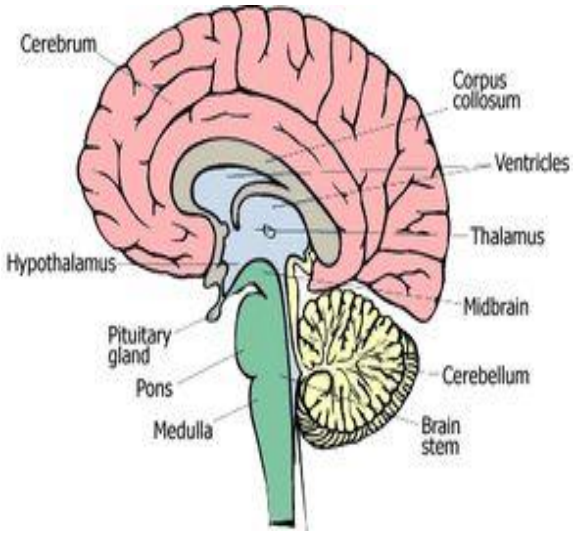

Fig. 2: Figure Showing Areas of Brain

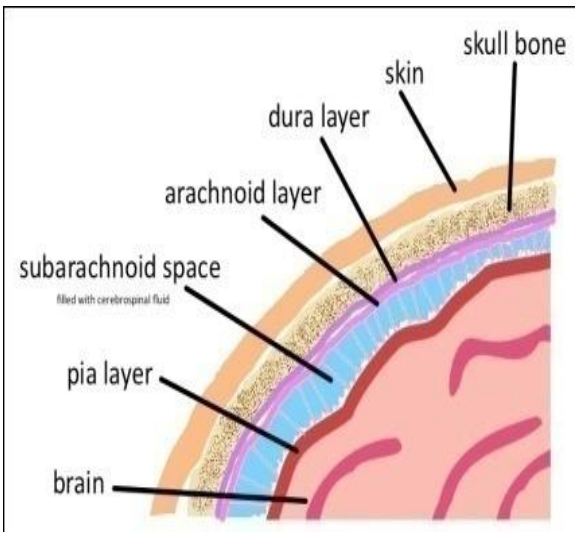

Fig. 3: Figure Showing Layers of Brain.

A) INCREASING PERMEABILITY OF DRUG THROUGH BBB [9-11]

Low molecular weight, unionized at physiological pH, and better lipophilicity require for better permeation from blood brain barrier. For example heroin crosses the BBB about 100 times faster than morphine due to its lipophilic nature. Hydrophilic drug can't cross BBB easily as compared with lipophilic drug. Incorporation lipophilic groups to hydrophilic drugs penetration of BBB enhances. The two techniques of drug permeation enhancement are:

(I) LIPOPHILIC APPROACH

Lipophilicity requires for the drug penetration through the BBB. The drug molecule should have Log P value of approximately 1.5 to 2.5 with an optimum octanol-water partition coefficient.

(II) PRODRUGS APPROACH

To improve the drug's pharmacokinetic properties prodrug form of them may be used. A prodrug consists of a drug covalently linked to an inert chemical moiety. The active drug is formed when the attached moiety in prodrug is cleaved by hydrolytic or enzymatic processes. In prodrugs the attaching chemical moieties should be such that it enhances the lipoidal nature of the drug. For example, various analogues of morphine. BBB is not readily crossed by morphine whereas acetylated product of morphine (heroin) readily traverses the BBB, and on subsequent cleavage of the acetyl groups by hydrolysis yields morphine. Hence in brain there is accumulation of morphine because of its hydrophilicity. Prodrug formation of a drug improves the brain uptake of drugs. For example, chemical modifications such as esterification of hydroxyl group, amidation of hydroxyl-, or carboxylic- groups of a drug, may increase the lipophilicity of drug and, as a result of which entry into the brain enhances.

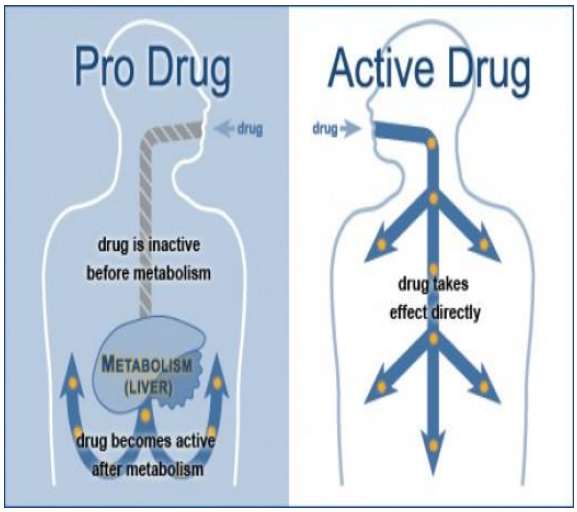

Fig. 4: Figure Showing Prodrug Concept.

B) CARRIERS DRUG DELIVERY SYSTEM [12-19]

There are various carriers system used in brain targeting. Some of
They include the following:

(I) LIPOSOMAL TECHNOLOGY

A liposome is a spherical vesicle having at least one lipid bilayer. The liposome can be used as a vehicle for administration of nutrients and pharmaceutical drugs. Liposome's are most often composed of phospholipids, especially phosphatidylcholine, but may also include other lipids, such as egg phosphatidylethanolamine, so long as they are compatible with lipid bilayer structure. A liposome design may employ surface ligands for attaching to unhealthy tissue. The major types of liposome's are the multilamellar vesicle (MLV, with several lamellar

phase lipid bilayers), the small unilamellar liposome vesicle (SUV, with one lipid bilayer), the large unilamellar vesicle (LUV), and the cochleate vesicle. A less desirable form are multivesicular liposome's in which one vesicle contains one or more smaller vesicles.Liposomes should not be confused with micelles and reverse micelles composed of monolayers.

LUVs and MLVs form by aqueous sucrose solution added slowly in the flask in slightly tilt position and drain over lipid surface layer. There is no need of rotation or stirring for swelling. MLVs are obtained on surface of suspension. Separate as a decant and remaining leaving LUVs in solution.

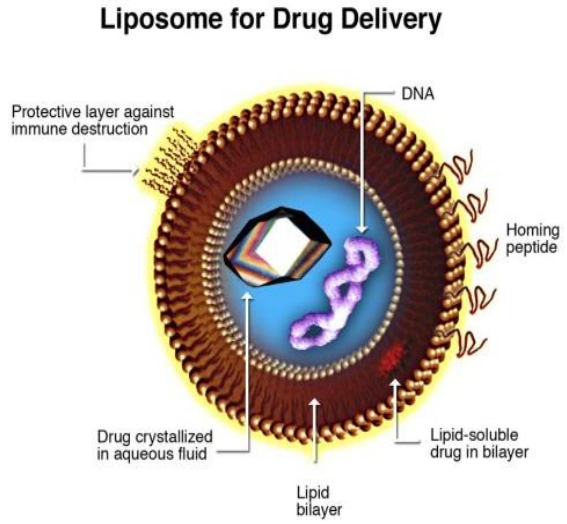

Fig. 5: Figure Showing Concept of Liposome Drug Delivery System.

(II) NANOTECHNOLOGY-

These are solids particles with ideal size range from 1 to 1000nm (1μm). They are made up of polymers in which drug loaded, encapsulated or entrapped. Example - Polyoxyethylene sorbitan monooleate coated nanoparticles containing drug given by I.V.Injection easily transport across the BBB. Those which low molecular weight can easily cross BBB as compared to high. The release of drug from nanoparticle depend upon the method of preparation and structure. Those nanoparticles prepare by surface modification may be absorbed by brain cells and hence, used for targeting BBB. Main advantage of this to reach API upto brain. By using nanotechnology we obtain maximum bioavailability across BBB in brain.

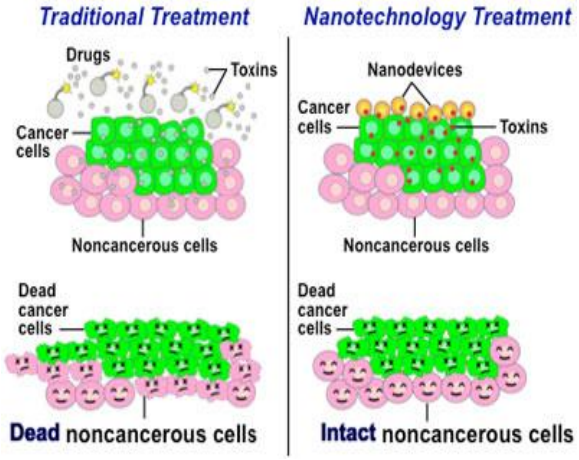

Fig. 6: Figure Showing Concept of Nanotechnology Drug Delivery System.

(III) MICROSPHERES

These are small spherical micron size solid particles, ranging from up to 1 to 1000 μm in size. Generally these are prepare by dispersing drug in various type of polymer e.g.- HPMC,Carbopol, Starch, Gelatin etc.These are prepared by coacervation phase separation, spray drying, solvent evaporation, emulsification, pan coating, polymerization. Most of the time these are used for Taste and Odour Masking agent, for control action, for protection of drug from external environment.

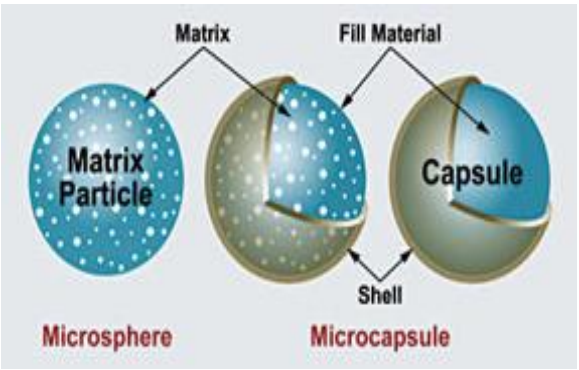

Fig. 7: Figure Showing Concept of Microsphere Drug Delivery System.

(IV) POLYMERIC MICELLES AND MICROEMULSIONS-

Micelles are formed by amphiphilic co-polymers with hydrophilic shell and hydrophobic core combinely formed structure called polymeric micelles. These micelles are chemically and physically stable in hydrophilic media. The ideal size ranges from 10 to 100 nm. For Example hydrophobic core polymer poly propylene glycol, poly (D, L-lactide) etc. and a hydrophilic shell polymers e.g., PEG. These are mainly biocompatible and biodegradable. As per review of brain targeting studied that poloxamer micelles conjugated with

antibodies may increase brain bioavailability of haloperidol, which is a neuroleptic agent. It indicates neuroleptic agents easily penetrate the BBB.

On other hand micro emulsions is a formulation which is used to increase solubility of poorly water soluble drugs hence increase the bioavailability of drug. It has globule size range from 1 -100 nm.

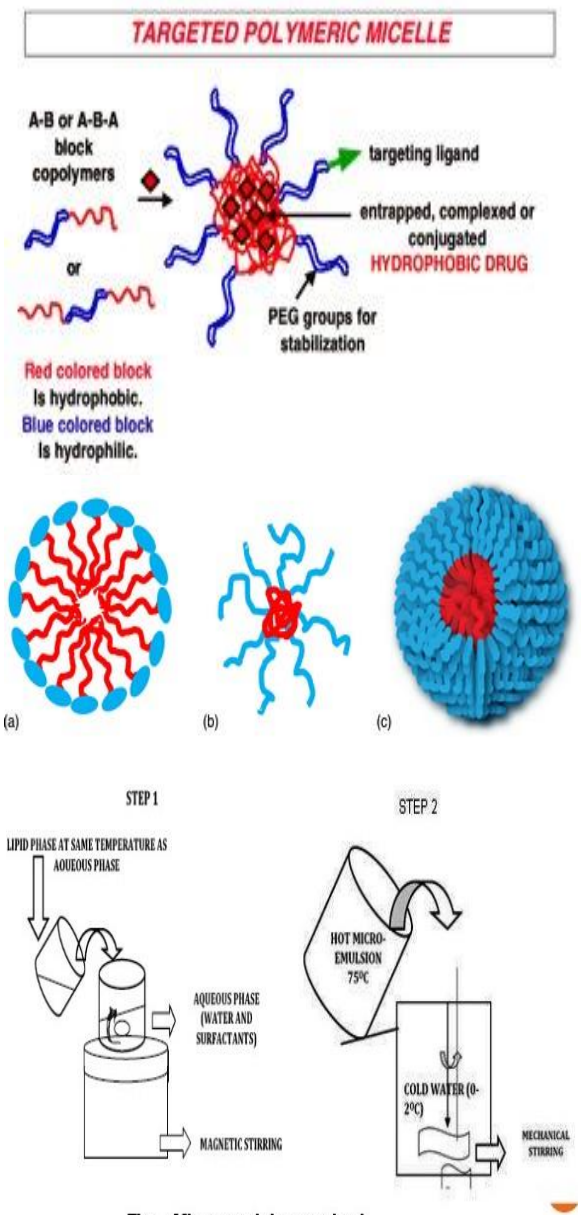

Fig. 8: Figure Showing Concept of Micelle and Micro emulsion Drug Delivery System.

(V) (VI) DENDRIMERS-

Dendrimers are a complex branched polymer molecule which consist of central core with branches are joined. The entire shell formed by branches attached with each other. These are of small size compare to that of nanoparticles and polymeric micelles of small in size. For example a dendrimer molecule, like as poly- amidoamine (PAMAM) dendrimer, has a size ranging from 1.5 - 14.5 nm. Dendrimers used as carrier for transportation of anticancer drugaccross the BBB, for the treatment of Central Nervous System carcinomas.

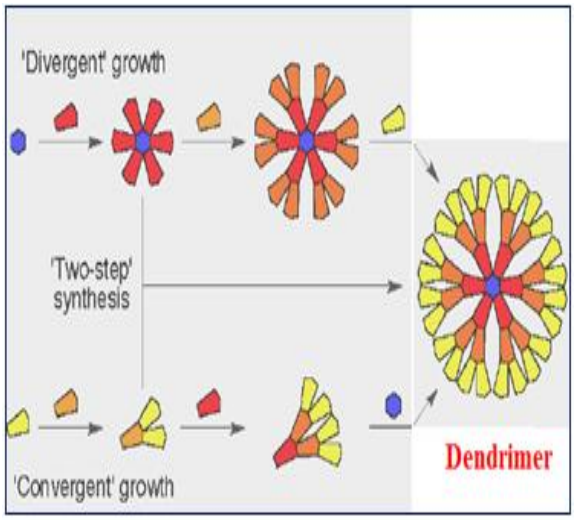

Fig. 9: Figure Showing Concept of Dendrimer Drug Delivery System.

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