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Brain targeting drug delivery system

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ABSTRACT

The prevalence rate for CNS pathology has demonstrated by approximately 1.5 billion people undergoing from disorders of CNS. Delivery of drugs to the CNS is the presence of blood brain barrier that has tendency to impair the drug distribution and it denotes the major impediment for the development of CNS drugs .In order to distribute the drugs into the CNS via passing the blood brain barrier, new emerging approaches have been developed for magnetic drugs targeting, chemical delivery system, and drug carrier system. The solid colloidal particles with a size range between 1-1000nm. In present it describes various nanotechnology based formulations such as polymeric nanoparticles, solid lipid nanoparticles, liposomes, dendrimers, micelles and nanoemulsions which widely used for better delivery of drugs across blood brain barrier. The net amount of delivered drug and its capability to gain access the main considering points for CNS drug development. Gradually the drug release reduced peripheral toxicity and potentiate to target at specific site and crossing the blood brain barrier are the major benefits to contributing the nanoparticles. The blood brain barrier is major challenge to deliver the drugs to CNS which limits the access of drugs to the brain substance. Strategies for drug delivery to brain involve by passing the blood brain barrier.

Keywords: Brain barrier, Drug delivery, Nanotechnology, Targeted drug delivery

INTRODUCTION

Brain is an important organ in human body which controls all body functions. In the CNS, the targeted action can be achieved by the direct administration of drugs into the CNS [1-2]. The large number of drugs can be impair the effect of blood brain barrier because of its hindrance effect. Any disorders or diseases related to brain are difficult to control because it is coated by the blood brain barrier. Blood brain barrier is usually does not cross by almost 100% of large molecule drugs and 98% of small molecule drug [3]. In advanced technology nanoparticles drugs delivery system can be utilized to delivery drug molecules directly in to the brain.

BLOOD BRAIN BARRIER

The blood brain barrier is the highly selective semi permeable membrane. The barrier that separates the circulating blood from the brain and extra cellular fluid in the central nervous system. The BBB is formed by brain endothelial cells and it allows the passage of water, some gases and lipid soluble molecules by passive diffusion [4]. The selective transport of molecules such as glucose and amino acids those are crucial to neural function. It prevents the entry of liphophilic potential neurotoxins by active transport mechanism mediated by P-glycoproteins. The blood brain barrier occurs along the capillaries and consists of tight junctions around the capillaries that do not exists in normal circulations. Actively transport metabolic products such as glucose across the barrier with specific proteins [5-6].

STRUCTURE

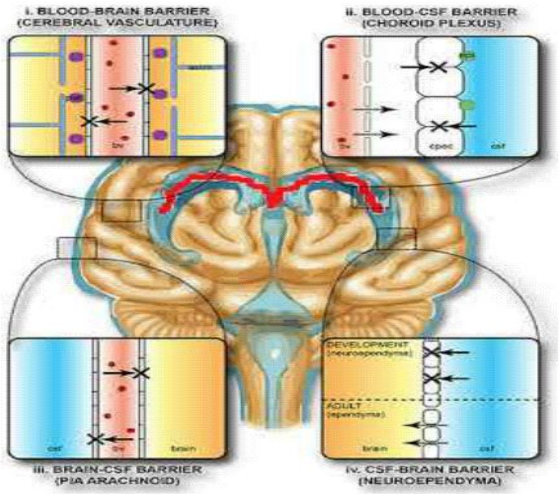

Fig no.1 Blood brain barrier

In blood brain barrier results from the selectivity of tight junctions between endothelial cells in CNS vessels, which restricts the passage of solutes. At the interference between blood and brain, endothelial cells are stitched together by these tight junctions, which are composed of small subunits. Biochemical dimmers, transmembrane proteins such as occludin, claudin, junctional adhesion molecules [7-10].

The blood brain barrier is composed of high density cells restricting the passage of substance from blood stream much more than the endothelial cells in capillaries in the body. Astrocyte cells projections called astriocytic feet's surrounding the endothelial cells of BBB, providing biochemical support to those cells. The blood brain barrier is quite similar to blood CSF barrier, which is a function of colloidal cells of the colloidal plexus [11-14].

TRANSPORT MECHANISM FOR BBB

Small liphophilic drugs, oxygen and carbon dioxide diffuse across the blood brain barrier, where ions require AT dependent transporters such as (Na+K) ATPase.Transporter for nutrients includes the glucose transporter GLUTi also known as solute carrier family, facilitated glucose transporter membrane (MCT1) and L1and Y+ transporters for large neutral and cationic essential amino acids transporters and excitatory amino acids transporter1 (EAAT1), EAAT2and EAAT3are located at the albuminal site [15]. The ATP binding cassette efflux transporters that are found in the endothelial cells include multidrug resistance protein and solute carrier organic anion transporter. Transporters for peptide or proteins include endothelial protein C-receptor for activated protein—C, the insulin and transferring receptors which are associated with caveolin, low density lipoprotein receptors related protein for amyloidB, peptide transport system for encephalins [16-18].

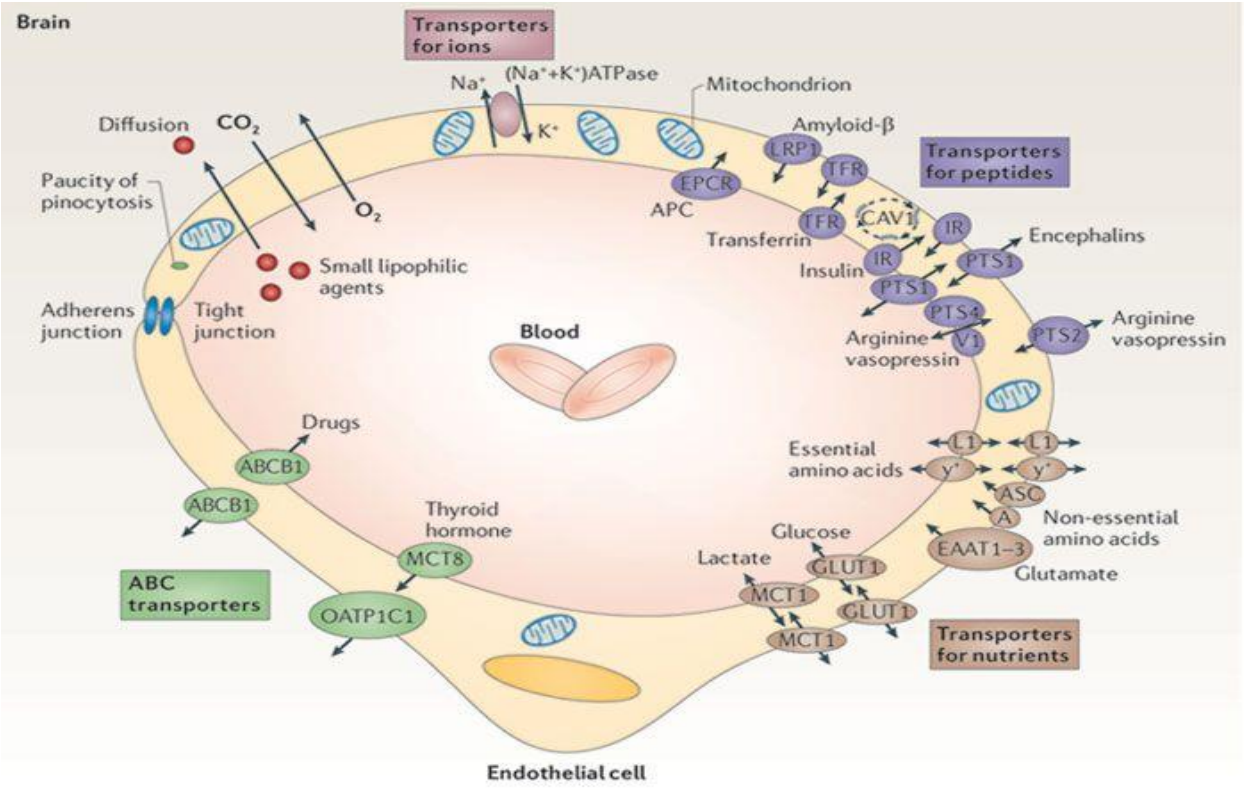

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Fig no.2 Mechanism of action of Blood brain barrier

TECHNIQUES

Pro drug approach

A pro drug consists of a drug covalently linked to the inert chemical moiety. The active drug is formed when the attached moiety in prodrugs is cleaved by hydrolytic or enzymatic process. In prodrugs the attaching chemical moiety should be enhances the lipoidal nature of the drug for example various analogues of morphine. BBB is not crossed by morphine where as acylated product of morphine transverse the BBB. In brain there is accumulation of morphine because of its hydrophilicity. Prodrugs formation of drug improves the brain uptake of drugs [19-22].

Liposomes

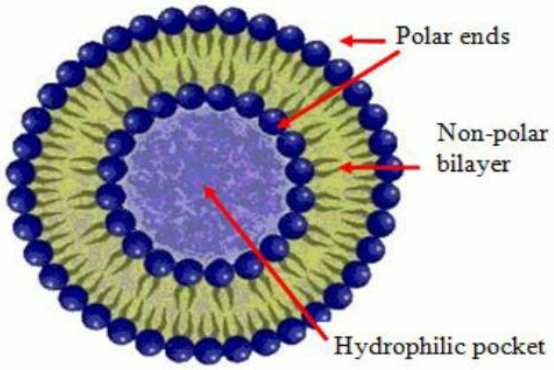


Fig no.3 Liposomes

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. Liposomes are composed of phospholipids, phosphatidylcholine, may also include other lipids such as eggphosphatidyl ethanolamine, so they are compatible with lipid bilayer structure [22-33]. A liposome design may employ surface ligands for acting to unhealthy tissues. The major types of liposomes are the multilamellar vesicles (MLV, with several lamellar phase lipid bilayers) the small unilamellar liposomes vesicles (SUV, with one lipid bilayer) the large unilamellar vesicle (LUV) and cochleate vesicles.

LUVs and MLVs form by aqueous sucrose solution added slowly in the flask in slightly and drain over lipid surface layer there is no need of rotations or stirring for swelling [24]. MLVs are obtained on surface of suspensions separate as a decant and remaining leaving LUVs in solution.

Dendrimers

Dendrimers are a complex branches polymer molecule which consists of central core with branches is 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 [25].

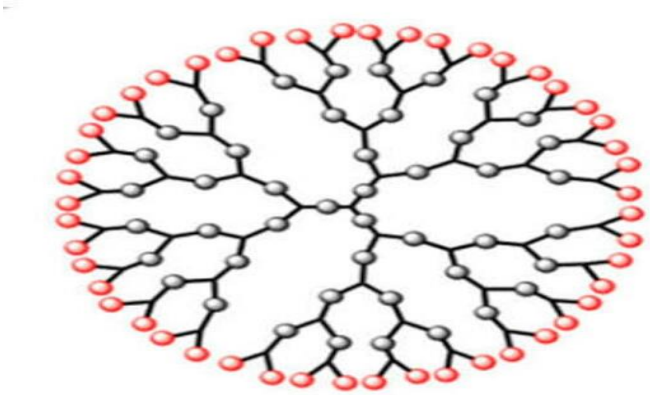
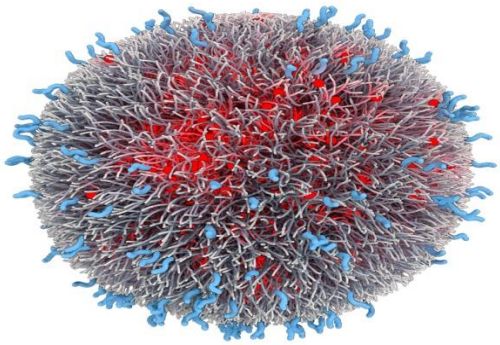


Fig no.4 Dendrimers

For example a dendrimers molecule like as P-amidoamine (PAMAM) dendrimers has a size ranging from 1.5-14.5nm. Dendrimers used as carrier for transportation of anticancer drug across the BBB, for the treatment of CNS carcinomas.

Nano particles



The term nanoparticles are used to designated the novel drug delivery system that are sub micron [<1micro metre] in size or colloidal systems. Nanoparticles constitute most vital element of nanotechnology including bionanotechnology.Nanoparticle is a broad class

comprises of both vesicular system [nanocapsules] and matrix systems [nanospheres]. Nanocapsules are systems in which the drug is confined to a cavity surrounded by unique polymeric membrane where as nanospheres are systems in which drug is dispersed throughout the polymer matrix apart from their basic structure nanocapsules differs from nanospheres in their size and degree of polymerization [26-28]. Nanocapsules are generally larger than nanospheres of same composition also the degree of polymerization is higher in nanocapsules as compared to nanospheres prepared by in-situ polymerization technique.

TYPES OF NANOPARTICLES TARGETING TO BRAIN

Lipid-based

Liposomes are composed of vesicular bilayers, lamellae, made of biocompatible and biodegradable lipids such as sphingomyelin, phosphatidylcholine and glycerophospholipids [67]. Cholestrol a type of lipid is also often incorporated in the lipid-nanoparticles formations [68]. Cholesterol can increased stability of liposomes and prevent leakage of bilayer because its hydroxyl group can interact with the polar heads of the bilayer phospholipids. Lipid nanoparticles can be manufactured by high pressure homogenization method used to produce parenterals emulsions. These manufacturing process is already scaled and use in the food industry which makes it more appealing for researches and for drug delivery industry.

Cationic liposomes

Cationic liposomes are lipid molecules that are positively charged.somes one example of cationic liposomes uses Bolaamphiphile, which contain hydrophilic groups surrounding a hydrophobic chain to strengthen the boundary of nanovesicle containing the drug .Bolaamphiphile nano-vesicles, can cross the BBB and they allow controlled release of drug to target sites. [66-67] Lipoplexes can also be formed from cationic liposomes and DNA solutions to yield transfection agents .Cationic liposomes cross the BBB through adsorption mediated endocytosis followed by internalization in endosomes of the endothelial cells.

Solid lipid

Solid lipid nanoparticles are lipid nanoparticles with a solid interior, solid lipid nanoparticles can be made by replacing the liquid lipid oil used in the emulsion process with a solid lipid. In solid lipid nano particles the drug molecules are dissolved in the particles solid hydrophobic lipid core. This is called the drug payload and it is surrounded by an aqueous solution. Many solid lipid nanoparticles are developed from triglycerides, fatty acids and waxes. High pressure homogenization or micro emulsification can be used for manufacturing. Further functionalizing the surface of solid lipid nanoparticles with polyethylene glycol can result in increased BBB permeability [70]

Polymeric micells

Polymeric micelles obtained from block copolymers as colloidal carriers for drug and gene targeting have been receiving attention in the field of drug delivery and targeting because of the high drug loading capacity [92]. A variety of drugs with diverse characteristics, including genes and proteins, can be incorporated in to the core. Researchers have demonstrated effective targeting of micelles systems to the brain by intravenous as well as intranasal route. [93]

Dendrimers

Dendrimers are a unique class of synthetic polymers which has a major role in nanotechnology advance of drug delivery [98]. The term “DENDRA” in “DENDRIMERS” is derived from Greek word which means tree and there for appropriately describes the architecture. Novel dendrimers based drug delivery systems consists of G3 polyamidoamine and surfactant conjugated dendritic nano conjugate successfully applied for targeted brain delivery [99]. Enhanced permeation of the lauryl modified G3PAMAM dendrimers. Paclitaxel conjugated across caco-2cell and PBEC monolayer’s has been demonstrated. Dendrimers conjugated had approximately 12 fold greater permeability across both cells monolayer’s than that of paclitaxelalone.

Liposomes

Nanoformulations such as liposomes consists of bilayer phospholipids systems in which water soluble drugs could reside in the aqueous phase enveloped by phospholipids bilayer and the

liphophilic drugs, could directly integrate into the membrane. Advanced version of liposomes such as long circulating liposomes, triggered release liposomes containing nucleic acid polymers, ligand targeted liposomes. Liposomes containing combination of drugs these advanced have lead to numerous clinical trials of anticancer drugs, antifungal drugs, antibiotics, gene medicines, anesthetics and anti inflammatory drugs. Targeted brain delivery using liposomal systems related in considerable increase of drug concentration in brain [100].

Major needs in brain drug targeting

1. Need to target therapeutics to specific brain regions or cell type.
2. Need to improve understanding of blood brain barrier transport system.
3. Need for in—vivo evaluation of brain drug pharmacokinetics.
4. Need to identify new brain drug targeting systems.
5. Need to speed development and applications of molecular imaging probes and targeted contrast agents.

Advantages of using nanoparticles for brain targeting

1. Protect the drug against chemicals and enzymatic degradization.
2. Accumulate at the targeted site.
3. The use of biodegradable materials allows sustained drug release at the target site after injection.

Limitations

1. Small size and large surface area particle-particle aggregation. Physical handlings of nanoparticles difficult in liquid and dry forms.
2. Small particles size and surface area readily result in limited drug loading burst release.

MARKETED FORMULATIONS

BRAND NAME	ACTIVE PHARMACEUTICAL INGREDIENT	ROLE
AMBISOME	AMPHOTERICIN-B	Liposomes for injection
CAELYX	PEGylated liposomal doxorubicin hydrochloride	Brain tumor
ARICEPT	DONEPEZIL	Alzheimer's disease
AURIMMUNE	Colloidal gold IV nanoparticles	Solid tumors
AUROSHELL	Gold coated silica nanoparticles	Solid tumors

Parameters considered crossing BBB

1. Compound should be unionized.
2. Approximately Log P value must be 2.
3. Its molecular weight must be less than 400Da.
4. Cumulative number of hydrogen bonds between 8-10.

Factors affecting drug delivery to brain

1. Concentration gradient of drug/polymer.
2. Molecular weight of the drug.
3. Sequestration by other cells.
4. Affinity for efflux proteins (Pgp).
5. Metabolism by other tissues.
6. Cerebral blood flow.
7. Systemic enzymatic stability.
8. Clearance rate of drug/polymer.
9. Pathological status.
10. Cellular enzymatic stability.
11. Liphophilicity of the drugs.

CONCLUSION

Now a day's many researchers are attracted towards brain targeting due to its immense applications in the treatment of various CNS diseases because mostly drugs are unable to cross the BBB. Nanotechnology has been developed to target the brain and possess various clinical benefits such as reduced drug dose, less side effects, on invasive routes and better patient compliance. The delivery of the drug molecules to the brain is precluded by a variety of physiological metabolite and biochemical abstracts the Blood brain barrier, Blood cerebro spinal fluid barrier, Blood testis barrier. In brain transport these systems also provide additional advantages such as extended or controlled release of drug and protection from degradation before reaching the target site leading to decrease dose or lesser frequency with decrease dose or no side effects.

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