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NANOPARTICLES AS SPECIFIED CARRIERS IN TARGETED BRAIN DRUG DELIVERY SYSTEM

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ABSTRACT

The blood brain barrier represents an insurmountable obstacle for a large number of drugs including antibiotics, anti neoplastics and a variety of CNS active drugs especially neuropeptides. One of the possibilities to overcome this barrier is a drug delivery to brain using nanoparticles. The use of nanoparticles to deliver drugs to the brain across the blood brain barrier may provide a significant advantage to current strategies. The primary advantage of nanoparticles carrier technology is that nanoparticles mask the blood brain barrier limiting the characteristics of the therapeutics, drug molecules and it also decreasing peripheral toxicity by causing slow drug release in the brain. The nanoparticles may be especially helpful for the treatment of the disseminated and very aggressive brain tumors. The mechanism of nanopraticles mediated transport of drugs is mostly endocytosis by endothelial cells lining the brain blood capillaries.

Keywords: Targeted drug delivery, Blood Brain Barrier, Central nervous system, Reticuloendothelium system, Neuroletics.

INTRODUCTION

The blood-brain barrier (BBB) protects the brain against toxic substances that circulate in the bloodstream. Although this is life-supporting protection for the brain, the existence of the BBB is a severe limitation for the delivery of most drugs to the brain because they do not cross the BBB in sufficient amounts. A large number of potentially useful drugs, such as cytostatics and central nervous system (CNS) active agents, do not cross the BBB at all or in insufficient quantities. However, for therapeutic reasons, methods to increase the bioavailability of drugs in the brain are needed to deliver drugs to the brain which are usually blocked from entering the brain by the BBB. One possible way to achieve this goal is to attach drugs to nanoparticles and thus transport them across the BBB. Nanoparticles are solid colloidal particles, ranging in size from 1 to 1000 nm (usually 200-300 nm), and they are a rather useful drug delivery system to target drugs to the brain. Here, we review the structure and the role of the BBB and describe the manner whereby molecules normally pass through the BBB. Furthermore, we will discuss how nanoparticles can be prepared and purified and review their physicochemical properties and drug release mechanisms. We then discuss the evidence that nanoparticles can be used to deliver drugs to the brain to overcome the limitation posed by BBB [1].

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 different polymers [3].
- 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 [4]:

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 nanoparticles are covered by the polymeric membrane.

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Advantages of Nanoparticles [5-8]

Nanoparticles are having several potential advantages over other carrier mediated drug delivery system.

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, which can be optimized property
2) May cause allergic reactions.
3) Over use of polyvinyl alcohol as a stabilizer may have toxic reactions.

TRANSPORT OF MOLECULES ACROSS THE BLOOD-BRAIN BARRIER

In some cases potentially useful compounds to treat brain disorders are injected into the bloodstream or given orally, but they do not reach the brain at all or not in sufficient amounts (insufficient bioavailability). Therefore, therapeutic efficiency to treat brain diseases is diminished or prevented because systemic administration of the drug does not lead to an effective brain concentration. There are many reasons why this may be the case: the molecules may be too large, they have unfavorable physiochemical properties (such as polar functional groups), they may be metabolized by enzymes before reaching their target (the brain), or they may be extruded at the cerebrovascular endothelium well before reaching the brain cells (neurons) upon which they should act. The major reason why drugs do not reach the brain is the existence of the BBB. To develop methods to overcome this barrier, a good understanding of its nature is required [10].

THE PHYSIOLOGY OF THE BLOOD-BRAIN BARRIER

The BBB is not one single structure or membrane in the brain, but it is created by the way the blood vessels in the brain are organized. Thus, understanding the BBB requires an understanding of the anatomy and physiology of the blood vessels in the brain. Both large and small capillaries form a richly branched and complex network throughout the entire brain tissue. Like a chimney made of individual bricks, the brain blood vessels consist of a monolayer of endothelial cells that are connected with each other by tight junctions. The part of the cells membrane facing the bloodstream is called the "luminal" membrane, and the side which is exposed to the actual brain tissue is called the "abluminal" membrane. This part faces the extracellular liquid of the brain parenchyma where pericytes and end feet of astrocytes surround the blood vessels. The most important site of the BBB lies at the cerebral micro vessels, that is, the very fine vessels that have extremely small diameters. Because endothelial cells are very polarized, that is, essentially similar to the epithelium, they exhibit very low pinorytic activity and possess a high number of mitochondria that are needed for the multiple energy-dependent active transport mechanisms found in endothelial cells.

Peripheral vessels in the rest of the body can much more easily transport molecules across their membrane because they are facilitated and have many active transcellular transport mechanisms. In contrast, in central blood vessels of the brain, even small molecules like antibiotics have great difficulty crossing the barrier and only a limited number of molecules can actively cross the endothelial cells. Here, the endothelial cells use specific transport systems to allow the influx of glucose, iron, amino acids, peptides, small organic acids, and others. This is necessary so that substances which are critical for brain metabolism and function can gain fast and efficient access to the brain via specific energy-dependent carrier mechanisms at the endothelium [1,11].

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 [12-14].
- 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.
- 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 [12,15]

- 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.
- Diffusion(Passive and active diffusion)
- Facilitated
- Active transport
- Transcytosis

Brain Targeting Technologyn[14]

- 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 liposome 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

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.

Enhancement of the Drug Transport [17]

The various approaches to enhance the drug transport across the BBB by means of nanoparticles,

1) Nanoparticles are preferably absorbed on the wall of the brain blood vessels without transport of particles across the endothelium.

2) The fluidization of the endothelium by the surface activity of the surfactant Polysorbate 80 enhances the drug transport across the brain.

3) Another possibility of the enhanced transport of the drug across the BBB is opening of the tight junction between the endothelial cells lining the brain.

4) At present the most likely mechanisms for the brain transport of drugs seems to be endocytic uptake by the endothelial cells lining of the brain blood vessels. These cells belong to classical reticuloendothelial system and are responsible for endocytosis of particulate matter under certain circumstances after endocytosis, delivery of the drug to the brain cells may occur by desorption of the drug from the nanoparticle with or without degradation of the nanoparticle.

5) Another approach for drug delivery to brain is trancytosis across the brain endothelial cells. After the uptake of the nanoparticle by the endothelial cells, the nanoparticles and adsorbed drug may be delivered to the other brain cells by trancytosis of nanoparticles.

6) The inactivation of p-glycoprotein flux pump would enhance the brain transport of nanoparticle. Drugs that have successfully been transported across this barrier by the nanoparticles include Dalargin, Loperamide and Tubocurarine.

Future aspects of brain targeting [19-21]

There are many technological challenges to be met, in developing the following techniques, 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 to be biocompatible and biodegradable because some sensitive drugs may prone to degradation. Nano particles to improve devices such as 'Implantable devices or Nan chips' 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.

Table 1. Different Types of Nanoparticles and Its Therapeutic Applications [9].

Nanoparticle component	Application	Indication
Liposomes	Drug delivery Drug delivery Drug delivery	Cancer Vaccines: influenza hepatitis A
Dendrimers	Therapeutics	Fungal infection, HIV, cancer, ophthalmology, inflammation.
Carbon nanotubes	In vitro diagnostics Imaging	Respiratory function monitoring, Atomic-force microscopy probe tip.
Quantum dots	In vitro diagnostics Imaging	Labelling reagents: Western blotting, flow cytometry, biodetection.
Magnetic nanoparticles,	In vitro diagnostics Imaging	Cancer, Liver tumours, cardiovascular disease.
Gold nanoparticles	TherapeuticsIn vitro diagnostics Imaging	Anaemia, Cancer.HIV Labelling reagents (PCR, RNA,Western blotting), angiography and kidney.

Table 2. Chemotherapeutic agents and transports across the brain [10].

Name	Characteristics	Transport across the BBB
Doxorubicin	Anthracyclins inhibits nucleic acid synthesis very narrow therapeutic index	-No
Paclitaxel	Microtubule-stabilizing	-No
Cisplatin	Inorganic Platinum ion complexes DNA alkylating and intercalating, short half life	-No
Iirinotecan	Inhibits DNA topo isomerase I induces single strand DNA lesions	-Yes
Methotrexate	Anti metabolite of folic acid inhibits dihydro folate reductase and DNA, RNA andprotein synthesis	-No
Carmustine	Alkylating agent	-No

THERAPEUTIC APPLICATION [18]

Table 3. Patents for nanoparticle based CNS targeted drug delivery systems

S. No.	Application	Summary of invention
1	Drug delivery in neurodegenerative Disorders	Nanoparticles loaded with epidermal growth factor
2	Targeting of drugs and diagnostic Agents	Conventional nanoparticles coated with surfactants to cross blood brain barrier
3	Drug delivery across blood brain Barrier	Nanoparticles prepared with addition of stabilizers during the polymerization Process
4	Drug delivery across blood brain Barrier	Drug loaded nanoparticles with coating of surfactant
5	Drug delivery across blood brain Barrier	Non-coated nanoparticles for brain targeting
6	Tumor targeting in brain	Metallic nanoparticles for brain targeting
7	Radiation therapy in brain	Surface coated nanoparticles with metallic core
8	Site specific drug delivery across Blood brain barrier	Nanogels prepared from cross-linked polyion polymer fragment and one nonionicwater soluble polymer fragment
9	Protein and peptide delivery to brain	Nanoparticles prepared from chitosan and polyglutamic
10	Drug delivery across blood brain Barrier	Nanoparticles prepared from protein coupled to apolipoprotein-e
11	Drug delivery across blood brain Barrier	Nanoparticles prepared from poly(DL-lactide) and poly(DL-coglycolide)
12	Drug delivery across blood brain Barrier	Large scale production of nanoparticles with single or multiple coating
13	Drug delivery across blood brain Barrier	Preparation of nanoparticles by mini-emulsion method
14	Inhibition of reperfusion injury to Brain	Nanoparticles prepared from inert inert plasticizers loaded with anti-oxidants
15	Brain delivery of oligonucleotides	Solid lipid nanoparticles
16	Delivery of drugs/ imaging agents across blood brain barrier	Functionalized solid lipid nanoparticles

17	Drug delivery across blood brain Barrier	Use of brain lipids for preparation of solid lipid nanoparticles.
18	Drug delivery across blood brain Barrier	Ex-vivo endocytosis of nanoparticles by a cell which is subsequently delivered to the brain
19	Drug delivery to either nucleus or cytoplasm of the cells including brain cells	Nanoparticles containing nuclear localization signal and capable of modulating gene expression/ protein expression
20	Treatment of solid tumors	Nanoparticles coupled with electromagnetic pulses/ ultrasound radiation
21	Tumor targeting in brain	Nanoparticles labeled with chlorotoxin
22	MRI of brain	Functionalized magnetic nanoparticles visible in MRI
23	Non-invasive Magnetic Resonance Angiography of brain	Fluorinated non-target nanoparticles that can yield both 2D and 3D images

Table 4. Patents pertaining to intranasal brain drug delivery using nanoparticles

Sl. No	Drug	Application Delivery	System
1	Neurotrophic Agents	Brain Disorders	-
2	Folic Acid, Cholinesterase	Alzheimer's Disease	-
3	NMDA Receptor Antagonist, MAO Inhibitor	Parkinson's Disease,Multiple Sclerosis, Alzheimer's Disease	Extended Release Dosage Form
4	Neurotrophic agents	Brain Disorders	Liposomes, Sustained Release Matrix, Lipid Based Micelles
5	Proteosomes	Glatiramer Neurodegenerative Disorders	Nanoemulsio
6	Clotrimazoe	Huntington's Disease	-
7	Huperzine-A	Senile Dementia	-
8	Diazepam	Epilepsy	Microemulsions
9	Benzodiazepines Valproic Acid Carbamazepine	Epilepsy	Nasoadhesive Microemulsions
10	Sedatives	Insomnia	Nasoadhesive Microemulsions
11	Triptans, Caffeine	Migraine	Nasoadhesive Microemulsions
12	Maps	immunomodulator	Dendrimer
13	Lorazepam	Epilepsy	Spray
14	Zolpidem	Insomnia	Cyclodextrin / Chitosan Sols

Figure 1. Schematic diagram of Nanosphere (A) and Nanocapsule (B) [5].

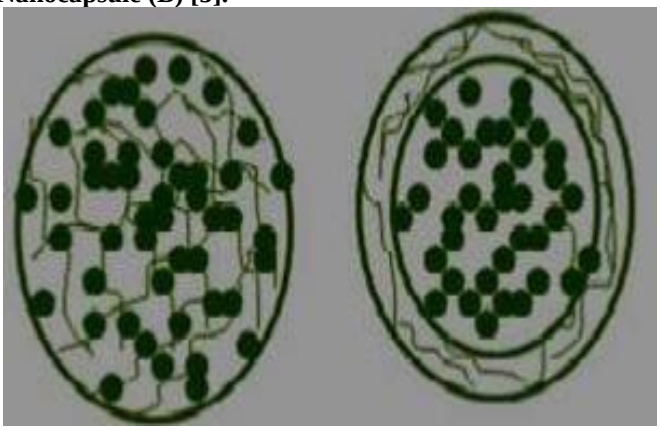
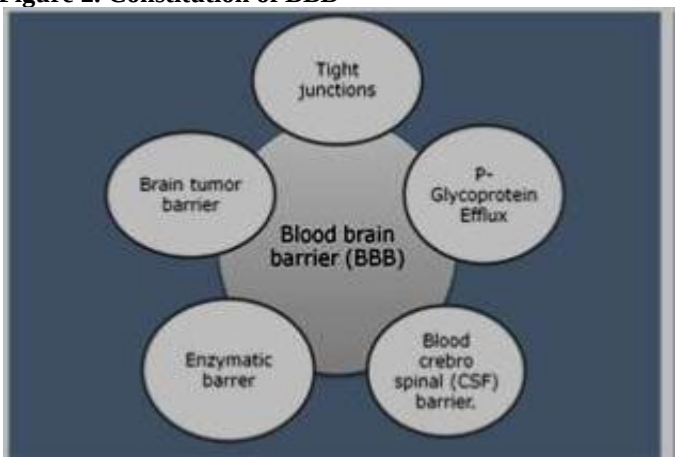


Figure 2. Constitution of BBB



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.

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