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A REVIEW OF NANOCARRIER-BASED CNS DELIVERY SYSTEMS

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Abstract:
Nanocarriers are nano-sized structures designed to transport and deliver various payloads, such as drugs or imaging agents, to specific targets within the body. They offer advantages like enhanced drug stability, controlled release, and targeted delivery, minimizing side effects. This abstract encapsulates the versatile applications and promising potential of nanocarriers in advancing drug delivery systems and medical treatments. These nanocarriers, often composed of lipids, polymers, or inorganic materials, enable precise control over drug release kinetics, improving therapeutic efficacy.
These nanocarriers, often composed of lipids, polymers, or inorganic materials, enable precise control over drug release kinetics, improving therapeutic efficacy. Their size and surface properties can be tailored for optimal interactions with biological systems, facilitating targeted delivery to specific tissues or cells. Furthermore, ongoing research explores multifunctional nanocarriers, integrating diagnostic capabilities or stimuli-responsive features, contributing to the evolution of personalized and efficient medical interventions.
Keywords: *nanocarriers, specific targets,polymers,lipids, inorganic domaterials, optimal interaction.*

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1.INTRODUCTION:

Nanocarriers, at the forefront of modern drug delivery, represent a paradigm shift in therapeutic interventions. These nano-sized vehicles, crafted from diverse materials, exhibit unparalleled precision in transporting and releasing payloads within the body. This introduction sets the stage to explore the intricate world of nanocarriers, delving into their composition, design principles, and transformative potential in revolutionizing drug delivery for enhanced efficacy and reduced side effects.

Within this realm, the ability to finely tune nanocarrier properties—ranging from size and surface characteristics to payload encapsulation—opens avenues for targeted and controlled drug delivery. As we embark on this exploration, we unravel the intricate strategies employed in engineering nanocarriers, spotlighting their promising applications across various medical domains. From oncology to infectious diseases, nanocarriers hold the promise of reshaping treatment modalities, offering a glimpse into a future where precision and efficiency converge for improved therapeutic outcomes.

Moreover, the review delves into the challenges and advancements surrounding nanocarrier technology, addressing issues such as biocompatibility, scalability, and regulatory considerations. As we journey through the intricacies of nanocarriers, a deeper understanding of their role in overcoming biological barriers and optimizing drug delivery kinetics emerges. This exploration not only underscores the current state of the field but also paves the way for envisioning the future trajectory of nanocarrier-based therapies, making this review an essential guide in navigating the evolving landscape of nanomedicine.

The failure of treatment in many instances is attributed not to the potency of the drugs, but to the various barriers that impede the efficient delivery of the drug to the brain interstitium. The delivery challenge is further amplified with newer generation of peptide, proteins, and oligonucleotides large molecular weight charged hydrophilic species – that have very poor diffusional properties in the biological milieu. Invasive drug delivery strategy has been the mostwidely used and was shown to be a clinically successful strategy for circumventing the blood-brain barrier (BBB) drug delivery problem [2]. In order to achieve non-invasive drug delivery to the CNS, many other attempts have been made. The most frequent and successful attempt is chemical modification of the drug or the transient opening of the BBB by osmotic method [5]. However, none of these methods can guarantee the desirable pharmacokinetic profile of the drug and in the latter case, the mechanism is non-specific, which can also enhance transport of potentially toxic agents from the blood into the brain during therapy.

The end of this paper is to review the current state- of the- art of these nanocarriers- grounded delivery systems for the CNS diseases. In order to understand the difficulties in medicine delivery to the CNS and appreciate the part played by these nanocarriers in circumventing those walls, it's necessary to compactly review the transport process in the CNS for medicine delivery. We'll compactly bandy the colorful walls that stymie the delivery of the medicines to the brain and also concentrate on the use of nanocarriers to manipulate these walls for effective delivery of medicines. For the purpose of this review

2. BARRIERS TO DRUG DELIVERY FOR THE CNS DISEASES-

The brain is a uniquely protected organ residing within the bony confines of the skull, thus making systemic delivery of drugs difficult. An obvious route of delivery would be via the cardiovascular system. The blood flow to brain is high, around 750-1000 mL/ min (about 15% of total cardiac output) [8]. Therefore, one would expect that such a high perfusion rate should be sufficient to deliver drugs into the brain. However, unlike the situation in most other organs, the cerebral blood compartment is not in free diffusional communication with the interstitium of the blood. Barrier layers are formed at three interfaces: blood vessels of the brain (blood brain barrier), the choroids plexus.

2.1. The Blood Brain Barrier-

The blood brain hedge consists of both anatomical and physiological factors. The blood capillary walls throughout the body are formed by a single subcaste of cells(Fig. 1). Generally, holes or pores between the cells making up the capillary wall permit free exchange of all tube factors, except the large tube proteins, with the girding interstitial fluid(Fig. 1 II and III). In the brain capillaries, still, the cells are joined by tight junctions, which fully seal the capillary wall so that nothing can be changed across the wall by passing between the cells. Also, glial cells called astrocytes compass about 85 of the face of the capillaries, adding a lipid hedge to the system. Astrocytes are allowed to be responsible for motioning the cells forming the brain capillaries to " get tight " and are also believed to share in the cross cellular transport of some substances(9, 11).

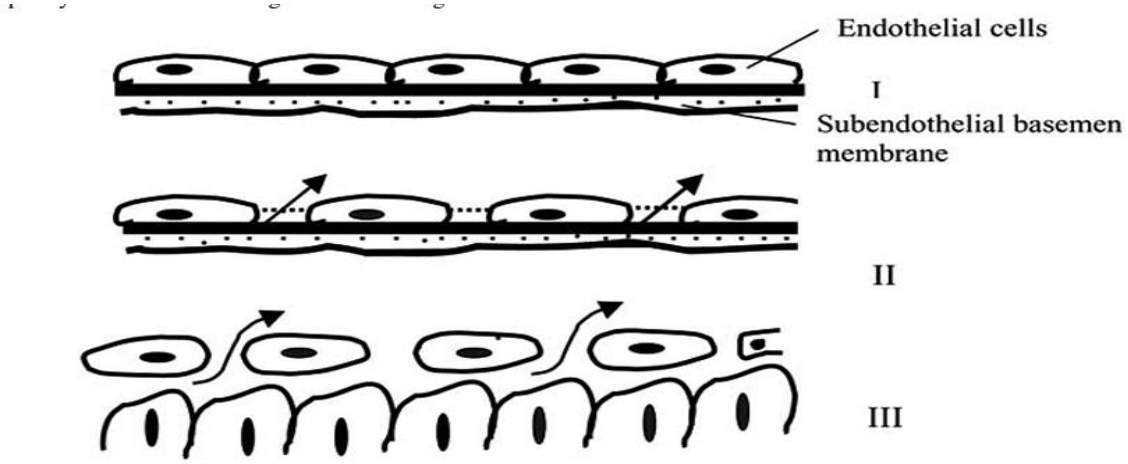

Fig-1 -Diagrammatic illustration of the structure of different classes of blood capillaries. I. Continuous capillaries. The endothelium is continuous with tight junctions between adjacent endothelial cells.

These transport processes result in these cells exhibiting considerably higher metabolic activity and utilizing substantially more energy than other cells in the body. To compensate for the higher energy requirement, the brain endothelial cells have nearly four times the mitochondrial content of the systemic endothelial cells [9]. (Fig-2)Some molecules that freely enter brain endothelial cells through the luminal membrane undergo rapid metabolic chemical transformations that inhibit them from crossing the antiluminal membrane and reaching the surrounding brain interstitium.

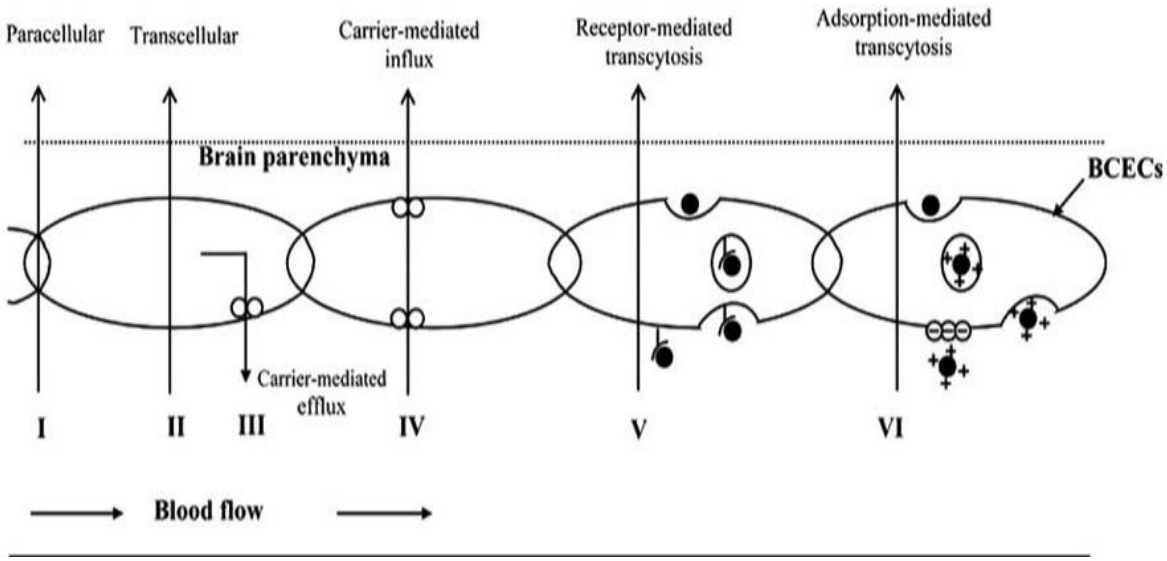

Fig-2-Transport routes across brain capillary endothelial cells, I. Paracellular pathway for diffusion of very small amounts of water soluble compounds; II. Transcellular pathway for diffusion of lipid soluble agents; III. Carrier mediated efflux pumps out some of the passively diffused lipophilic molecules; IV. Carrier mediated influx transports essential polar solutes such as glucose, amino acids, nucleosides, monocarboxylates and small peptides; V. Essential proteins such as insulin, transferrin and cytokines are transported by specific receptor mediated transcytosis VI.

Compared to systemic endothelial cells, cerebral endothelial cells have a marked deficiency in pinocytic vesicles. These vesicles are important for the extravasation of molecules (and bulk flow fluid movement) that are otherwise unable to traverse tightly fused endothelial sheets [9, 14]. The apparent paucity of these vesicles in the CNS provides an even greater selectivity to the cerebral capillary

endothelium [10, 13, 14]. Furthermore, blood brain barrier is armed with P-glycoprotein (Pgp), an ATP-binding cassette family of active drug efflux transporter pump. Pgp is present in high density in the luminal membrane of the brain endothelium [13, 15]. This efflux transporter actively removes a broad range of structurally unrelated drug molecules from the endothelial cell cytoplasm before they can cross into the brain parenchyma. Thus, although some cytotoxic agents used to treat brain tumors, such as vincristine and vinblastine, penetrate the luminal membrane, they are then pumped out by the Pgp transporter, effectively excluding them from the brain parenchyma. This transporter appears to have a very broad specificity with no clear rules yet available on the quantitative structure-activity relationships (QSAR) for the transport site(s). The constitutive role of Pgp in the normal BBB is inferred to be a protective one by reducing entry of lipophilic and neurotoxic substances into the CNS

2.2. The Blood Cerebrospinal Fluid Barrier-

The blood–CSF barrier is at the choroids plexus and other CVO's. Choroid plexuses are networks of capillaries (microscopic blood vessels) in the walls of the two lateral ventricles. The capillaries are covered by ependymal cells that form cerebrospinal fluid from blood plasma by filtration and secretion. Because the ependymal cells are joined by tight junctions, materials entering CSF from choroids capillaries cannot leak between these cells. Rather, they must go through the ependymal cells. This bloodcerebrospinal fluid barrier permits certain substances to enter the fluid but excludes other. Such a barrier protects the brain and spinal cord from potentially harmful substances in the blood. Because the CSF can exchange molecules with the interstitial fluid of the brain, the passage of blood-borne molecules into the CSF is carefully regulated by the bloodCSF barrier. Once CSF is formed, it is rapidly moved by bulk flow over the cerebral convexities and reabsorbed into the general circulation at the upper regions of the brain through the arachnoid villi .

The relative surface area of the choroids plexus epithelium, which forms the blood CSF barrier, compared to the tight BBB is 1:1000 [16]. It is apparent that the extent to which a given molecule in blood enters brain parenchyma is determined solely by the permeability characteristics of the BBB. The distribution of circulating drug into brain via the transport through the blood CSF barrier followed by diffusion into brain is minimal, owing to rapid export of drugs and solutes from CSF to blood. Furthermore, the BBB and blood-CSF barrier are anatomically and functionally distinct [11]. Consequently, the type of transporters expressed on the plasma membranes at these two barrier systems is quite different and a given drug may cross the blood-CSF barrier, and enter CSF readily, but could be prevented from crossing the BBB or enter brain interstitial fluid.

3. NANOCARRIER-BASED DELIVERY IN THE CNS-

3.1. Liposomes-

Since their discovery by A.D. Bangham in the 1960s, liposomes have received much attention as drug carriers [1725]. Conventional liposomes resemble plasma membranes, consisting of phospholipids molecules with a polar head with two hydrophobic tails forming a bilayer. Liposomes can be prepared with diameters ranging from 20 nm to 100 µm. They are classified according to their final size and preparation method in; SUV, small unilamellar vesicles (20-50 nm); LUV, large unilamellar vesicles (100 nm); REV, reverse phase evaporation vesicles (0.5 µm); MLV large multilamellar vesicles (2-10 µm) [26]. Liposomes are biocompatible, nontoxic and biodegradable and offer possibility of carrying hydrophobic, hydrophilic, and amphiphilic molecules. As liposomes are highly lipophilic in nature, one would expect them to be the ideal carrier systems for targeting the BBB, where liposomes can transport their contents to the brain parenchyma either by passive diffusion through the lipophilic endothelial cells, by fusion with the brain capillary endothelial cells, or by endocytosis (Fig. 2). Different types of liposomal formulations have been employed for transporting drugs across the BBB (Fig. 3).

Initial studies employing very large liposomes were quite unsuccessful in transporting drugs across the BBB. When fluroscein or trypan blue were encapsulated in liposomes and injected intravenously, they stained only the luminal side of the vasculature and not the abumenal side or brain parenchyma, indicating failure of liposomes to cross the BBB [27]. After recognizing that the relatively large size of liposomes i.e., 0.2- 1.0 µm was responsible for rapid ingestion by the cells in the reticuloendothelial system (RES), particularly in liver and spleen, liposomes were subsequently designed that were small unilamellar vesicles (SUVs), which ranged from 0.025 to 0.1 µm in diameter [26]. The use of SUV liposomes was found to greatly retard the rate of clearance from blood as compared with large vesicles. Subsequently, most of the research on liposomes for the BBB delivery has focused on the use of these SUVs

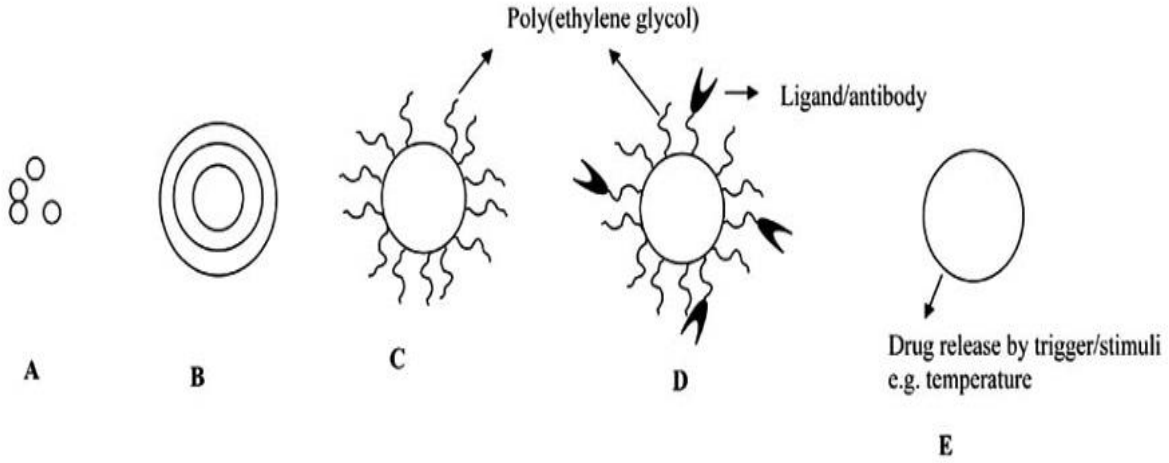

Fig-3-Types of liposomes used for transporting drugs to CNS. A. Small unilamellar vesicles (SUVs); B. Multilamellar vesicles (MLV), C. PEGylated or PEG coated liposomes; D. PEGylated ligand/antibody bearing Immunoliposomes. E. Stimuli sensitive liposomes.

A promising method for the delivery of compounds that are unable to pass the BBB by themselves is the use of transport vectors, which activate natural transport routes. The development of vectors arises from an understanding of the pathway of solute transport such as either carrier mediated (e.g., for nutrients) or receptor mediated (e.g., for peptides) (Fig. 2). Specific receptors on brain capillaries have been identified for transferrin, insulin, and insulin-like growth factors [13]. Coupling of vectors to liposomes combines the advantages of targeting, incorporation of drugs at high concentration, reduced side effects, and circumvention of the multidrug efflux system. An additional advantage is provided by sterically stabilized liposomes modified with PEG chains. They have a distinctly prolonged circulation time in the blood stream compared to conventional liposomes. The success of the strategy of vector-carrier coupling for brain targeting has been documented with immunoliposomes, which are transported across the BBB via receptor-mediated endocytosis or the efficient uptake of cationized albumincoupled liposomes by brain capillaries via adsorptive endocytosis.

3.2. Polymeric Nanoparticles

Nanoparticles are defined as solid colloidal particles made of polymeric materials ranging in size from 1-1000 nm [6, 75, 76]. They are used as drug carrier system in which the active compound is dissolved, entrapped, encapsulated and /or to which the active compound is adsorbed or attached. Examples of synthetic polymers used to prepare nanoparticles are poly(methylmethacrylate), poly(alkylcynoacrylate), acrylic copolymers, poly(D,L-lactide-co-glycolide), and poly(lactide) [77]. Nanoparticles have also been produced from natural proteins (albumin and gelatin) and polysaccharides (dextran, starch, and chitosan). Like liposomes, nanoparticles are rapidly cleared from the blood following intravenous administration and >90% of the nanoparticles are removed from the blood stream within 5 min in mice [16, 78]. Several attempts have been made to change biodistribution of nanoparticles. The most promising results were obtained by coating particles with hydrophilic surfactants, which significantly altered pharmacokinetics and biological distribution of nanoparticles or by the covalent.

A recent study has demonstrated the BBB transport of nerve growth factor (NGF) using poly(butylcyanoacryate) nanoparticles coated with polysorbate-80 [89]. Systemic administration of NGF adsorbed on PBCA-nanoparticles coated with polysorbate-80 successfully reversed scopolamine-induced amnesia and improved recognition and memory in acute amnesia rat model. This appeared in the form of a significant increase in the mean latent period of passive avoidance reflex test in the group of animals treated with NGF adsorbed on PBCA-nanoparticles coated with polysorbate-80 compared with the group treated with free NGF. In addition to surfactant coating, PEGylation of cynoacrylate nanoparticles has also been reported for circumventing the BBB [83]. Nanoparticles of amphiphilic block copolymer, PEG and hexadecylcynoacrylate (PEG-PHDCA) were prepared and their ability to diffuse into the brain tissue was evaluated in mice and rats after intravenous administration. Results indicated that

PEGylated PHDCA nanoparticles penetrated into the brain to a larger extent than polysorbate 80- or poloxamine 908-coated PHDCA nanoparticles, and the uncoated PHDCA nanoparticles. Epifluroscent microscopy studies showed that the nanoparticles were localized in the ependymal cells of the choroid plexuses, in the epithelial cells of pia mater and ventricles, and to a lower extent in the capillary endothelial cells of the BBB. Poloxamine 908coated nanoparticles failed to diffuse into the brain tissue.

3.3. Solid Lipid Nanoparticles-

Besides solid polymeric nanoparticles, solid lipid nanoparticles (SLN) have also been employed to circumvent the BBB. Solid lipid nanoparticles are dispersions of solid lipids stabilized with emulsifier or emulsifier/co-emulsifier complex in water [100, 109, 110]. Solid lipids used to prepare SLN include widely used food lipids and waxes (e.g. cetyl palmitate) and commonly used emulsifiers include different kinds of poloxamers, polysorbates, lecithin, and bile salts.

To achieve specific targeting to brain, emulsifying wax nanoparticles were coated with thiamine for efficient cell binding. The results showed that surface modification with thiamine enhanced the interaction of the nanoparticles with the cells due to specific association with the BBB thiamine transporter and it was postulated that such an association may create an accumulation of nanoparticles at the BBB, which may ultimately increase the drug uptake over the period of time [97]. The mechanism of drug transport enhancement mediated by nanoparticles into the brain is still not fully understood. Various mechanisms have been proposed in literature for the BBB transport of polymeric solid and lipid nanoparticles and it is possible that combination of some or all of the mechanisms are acting to facilitate transport.

4. CONCLUSIONS:

Nanocarriers offer a promising platform for central nervous system (CNS) drug delivery systems. Their ability to traverse the blood-brain barrier and target specific sites within the CNS holds great potential for improving the efficacy of therapeutic interventions. However, further research is essential to address challenges such as long-term safety, scalability, and optimization of drug loading. As we continue to unravel the complexities of nanocarrier-based CNS delivery, it opens new avenues for developing innovative treatments for neurological disorders.
Additionally, the versatility of nanocarriers allows for customization in terms of size, surface properties, and composition, enabling tailored approaches for different therapeutic applications. The controlled release capabilities of these carriers contribute to minimizing side effects and optimizing drug concentrations in the CNS. Despite these advancements, the clinical translation of nanocarrier-based CNS delivery systems necessitates thorough preclinical studies and rigorous testing to ensure safety and efficacy.

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