Review Article

Novel Approaches for Brain Drug Delivery System-Review

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ABSTRACT

The brain is a delicate organ, and nature has very efficiently protected it. Drug delivery into the brain was difficult due to the existence of blood brain barrier, which only permits some molecules to pass through freely. The brain is shielded against potentially toxic substances by the presence of two barrier systems: the blood brain barrier (BBB) and the blood cerebrospinal fluid barrier (BCSFB). Unfortunately, the same mechanisms that protect it against intrusive chemicals can also frustrate therapeutic interventions. In past decades, nanotechnology has enabled much technical advancement, including drug delivery into the brain with high efficiency and accuracy. The challenging domain of effective brain delivery has led to a keen scientific pursuit and as a result many novel methods have been invented and patented. In the present paper, we summarize recent important advancements in employing nanotechnology for drug delivery. The technological strategies are essentially non-invasive methods of drug delivery to malignancies of the central nervous system (CNS) and are based on the use of nanosystems (colloidal carriers) such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, polymeric micelles and dendrimer. Based on the current findings, it can be concluded that crossing of the BBB and drug delivery to CNS is extremely complex and require a multidisciplinary approach such as a close collaboration and common efforts among researchers of several scientific areas, particularly medicinal chemists, biologists and pharmaceutical technologists.

Keywords: Blood-brain barrier, nanoparticle, liposome, polymeric micelles and micro emulsions, molecular trojan horses.

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INTRODUCTION

The central nervous system is protected by BBB, BCF, and BTB which control the entry of compounds into the brain, thereby regulating brain homeostasis. Barrier restricts access to brain cells of blood–borne compounds and facilitates nutrients essential for normal metabolism to reach brain cells. This regulation of the brain homeostasis results in the inability of some small and large therapeutic compounds to cross the blood–brain barrier (BBB). Therefore, various strategies have been developed to enhance the amount and concentration of therapeutic compounds in the brain [1].

The brain is shielded against potentially toxic substances by the presence of two barrier systems: the blood brain barrier (BBB) and the blood cerebrospinal fluid barrier (BCSFB).

It is estimated that more than 98% of small molecular weight drugs and practically 100% of large molecular weight drugs (mainly peptides and proteins) developed for CNS pathologies do not readily cross the BBB and discovery of new modalities allowing for effective delivery of drugs and bio macromolecules to the central nervous system (CNS) is of great need and importance for treatment of neurodegenerative disorders (Alzheimer's disease, Epilepsy) [2]. This manuscript focuses on three relatively new strategies. The first strategy involves inhibition of the

drug efflux transporters expressed in BBB by Pluronic® block copolymers, which allow for the increased transport of the substrates of these transporters to the brain. The second strategy involves around the design of nanoparticles conjugated with specific ligands that can target receptors in the brain microvasculature and carry the drugs to the brain through the receptor mediated transcytosis. The third strategy involves artificial hydrophobization of peptides and proteins that facilitate the delivery of these peptides and proteins across BBB [3].

The parameters considered optimum for a compound to transport across the BBB are:

- Compound should be unionized.
- Approximately logP value must be 2.
- Its molecular weight must be less than 400 Da.
- Cumulative number of hydrogen bonds must not go beyond 8 to 10.

It is estimated only 2% of small molecular weight drug will across BBB.

BARRIERS TO CNS DRUG DELIVERY

The failure of systemically delivered drugs to effectively treat many CNS diseases can be rationalized by considering a number of barriers that inhibits drug delivery to the CNS.

Blood-Brain Barrier (BBB)

Basal membrane and brain cells, such as pericytes and astrocytes, surrounding the endothelial cells further form and maintain an enzymatic and physical barrier known as the blood–brain barrier (BBB).

BBB tight junctions are formed between endothelial cells in brain capillaries, thus preventing paracellular transport of molecules into the brain.

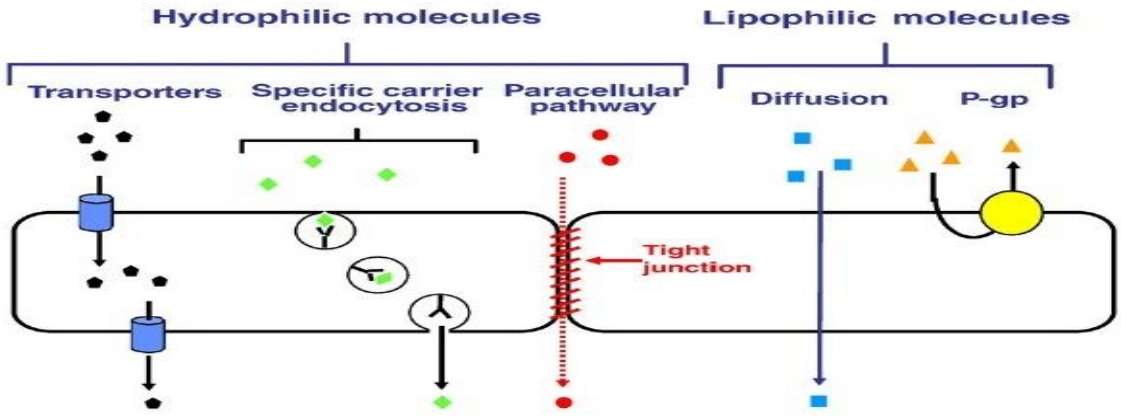

Fig. 1: Schematic representation of the transport of molecules across the BBB

Micro-vessels small in diameter and thin walls compared to vessels in other organs make up an estimated 95% of the total surface area of the BBB, and represent the principal route by which chemicals enter the brain. In brain capillaries, intercellular cleft, pinocytosis, and fenestrate are virtually nonexistent; exchange must pass trans-cellularly. Therefore, only lipid-soluble solutes that can freely diffuse through the capillary endothelial membrane may passively cross the BBB [4].

Blood–cerebrospinal fluid barrier (BCSFB)

Another barrier between the blood and the brain is the blood–cerebrospinal fluid barrier (BCSFB), which separates the blood from cerebrospinal fluid (CSF). However, this barrier is not considered as a main route for the uptake of drugs since its surface area is 5000-fold smaller than that of the BBB [5–8].

CSF can exchange molecules with the interstitial fluid of the brain parenchyma; the passage of blood-borne molecules into the CSF is also carefully regulated by the BCB. Physiologically, the BCB is found in the epithelium of the choroids plexus, which is arranged in a manner that limits the passage of molecules and cells into the CSF [9-11].

The choroid plexus and the arachnoid membrane act together at the barriers between the blood and CSF [12].

The arachnoid membrane is generally impermeable to hydrophilic substances, and its role is formation of the Blood-CSF barrier, is largely passive. The choroid plexus forms the CSF and actively regulates the concentration of molecules in the CSF.

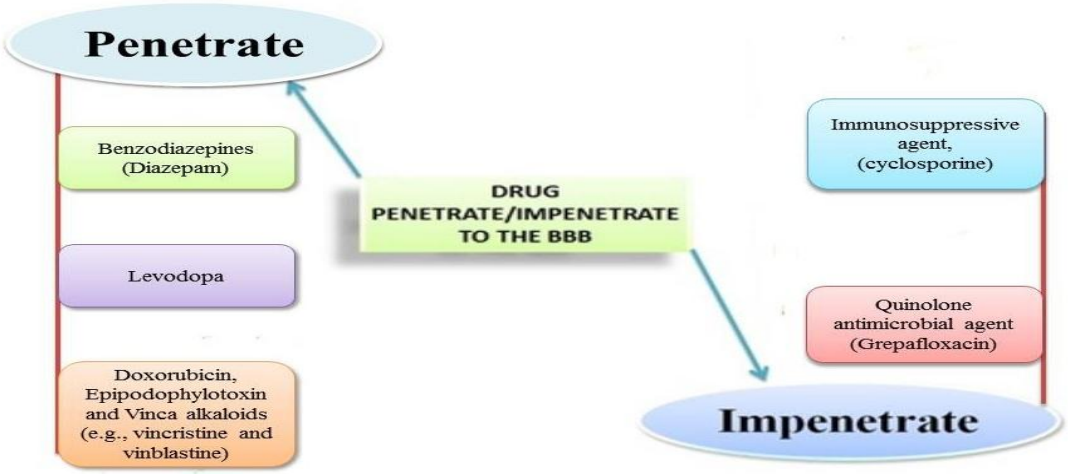

Fig. 2: Schematic representation of the drug penetrate and impenetrate across the BBB.

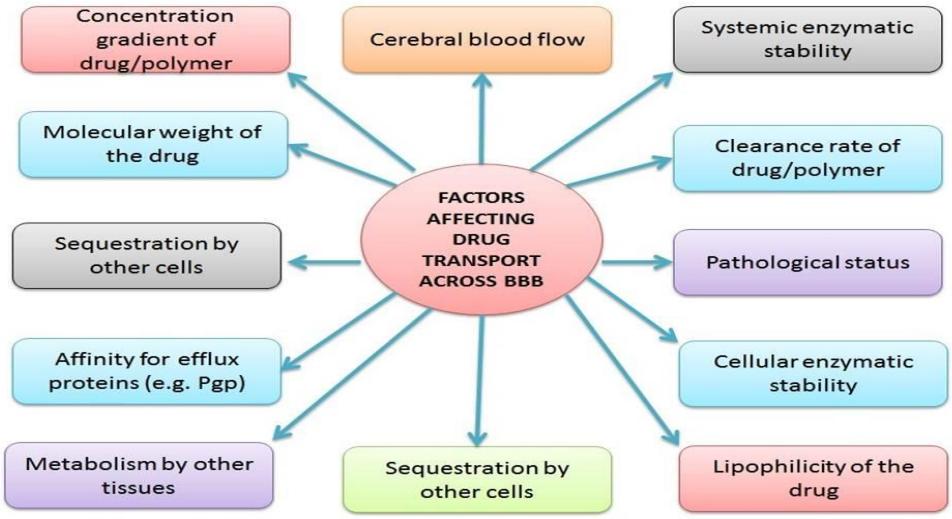

Fig. 3: Schematic representation of the factors affecting drug transport across the BBB

3-Blood-Tumor Barrier

Intracranial drug delivery becomes even more challenging when the target is a CNS tumor. The presence of the BBB in the microvasculature of CNS tumors has clinical consequences (13).

In CNS malignancies where the BBB is significantly compromised, a variety of physiological barriers common to all the solid tumors inhibit drug delivery via the cardiovascular system. Drug delivery to neoplastic cells in a solid tumor is compromised by a heterogeneous distribution of microvasculature throughout the tumor interstitial, which leads to spatially inconsistent drug delivery. However, as a tumor grows large, the vascular surface area decreases, leading to reduction in trans-vascular exchange of blood-borne molecules. At the same time, intra-capillary distance increases, leading to a greater diffusional requirement for drug delivery to neoplastic cells and due to high interstitial tumor pressure and the associated peri-tumoral edema leads to increase in hydrostatic pressure in the normal brain parenchyma adjacent to the tumor. As a result, the cerebral microvasculature in these tumor adjacent regions of normal brain may be even less permeable to drugs than normal brain endothelium, which leads to exceptionally

low extra-tumoral interstitial drug concentrations [15].

Brain tumors may also disrupt BBB, but these are also local and non homogeneous disruptions [16].

APPROACHES TO CNS DRUG DELIVERY

Basically, two methods have been described in the literature to actively enhance drug delivery to the brain after systemic administration: either opening/disruption of the neuroprotective BBB by osmotic imbalance, ultrasound or vasoactive compounds (e.g., bradykinin or P-glycoprotein inhibitors), or physiological strategies aiming to use endogenous transport mechanisms. While the first method has the disadvantage that those neurons may be damaged (semi)-permanently due to unwanted blood components entering the brain [17-21]. The physiological strategies have a large potential as discussed in several review papers elsewhere [22]. As a third alternative (using a combination of aspects of both methods), positive charge has also been applied to compounds or drug carriers to quite effectively enhance the absorptive-mediated transport across the BBB [23-24]; however, a beneficial therapeutic window of this basically toxic transport mechanism has thus far not been established.

To overcome the multitude of barriers restricting CNS drug delivery of potential therapeutic agents, numerous drug delivery strategies have been developed. These strategies generally fall into one or more of the following categories: invasive, non-invasive or miscellaneous techniques [27-29].

The CNS drug delivery tree encompassing the various possible strategies is shown below in the (**Fig. 4**).

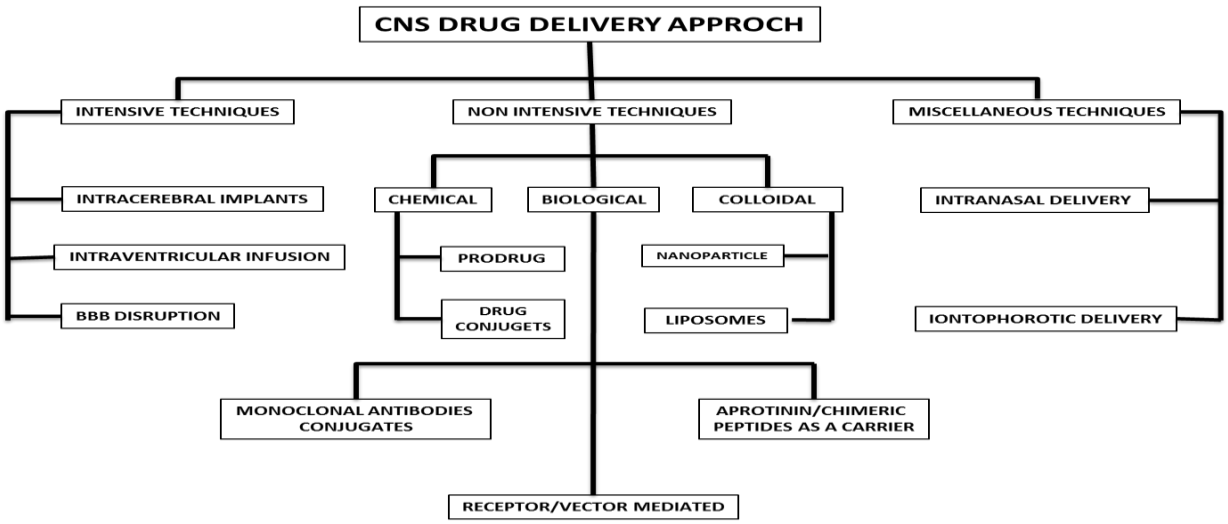

Fig. 4: Schematic representation of the different drug delivery approaches to the CNS.

PHARMACEUTICAL TECHNOLOGY-BASED STRATEGIES

The technological strategies are essentially non-invasive methods of drug delivery to the CNS and represent valuable approaches for enhancing transcellular permeability of therapeutic agents and biomacromolecules across the BBB. They are based on the use of nanosystems (colloidal carriers), mainly liposomes and polymeric nanoparticles even though other systems such as solid lipid nanoparticles, polymeric micelles and dendrimers are also being tried.

An important requirement of the systemic intravenous use of these nanocarriers is their ability to circulate in the bloodstream for a prolonged period of time. However, after intravenous administration, they interact with the reticuloendothelial system (RES) which removes them from the blood stream.

This process mainly depends on particle size, charge and surface properties of the nanocarrier [25-26].

To prevent the uptake by the RES, poly ethylene glycol (PEG) coating or direct chemical linking of PEG to the particle surface provides relatively long plasma

residence times.In fact, thesenanocarriers can be taken up actively by carrier–mediated transport (CMT), receptor-mediated endocytosis (RME) and adsorptive-endocytosis (AME) and hence reaches the cerebral parenchyma, or is degraded within lysosomes leading to the drug being released into the brain tissues.

Liposomes

Liposomes are small vesicles (usually submicron-sized) comprising of one or more concentric bilayers of phospholipids separated by aqueous compartments. It has also been suggested that liposomes could enhance drug delivery to the brain across the BBB. Although liposomes have been reported to enhance the uptake of certain drugs into the brain after intravenous injection.

Liposomes are sterically stabilized by attaching ligands to the surface of the liposomes [28-29].

A recent application of transferrin surface-conjugated liposomes includes the delivery of the anticancer drug 5- fluorouracil (5-FU) to brain. 5-FU is one of the most powerful anticancer agents, but cannot reach an effective concentration in the brain tumor cells when administered systemically.

Modified liposomes have also been used for enhanced gene delivery to brain tumors.

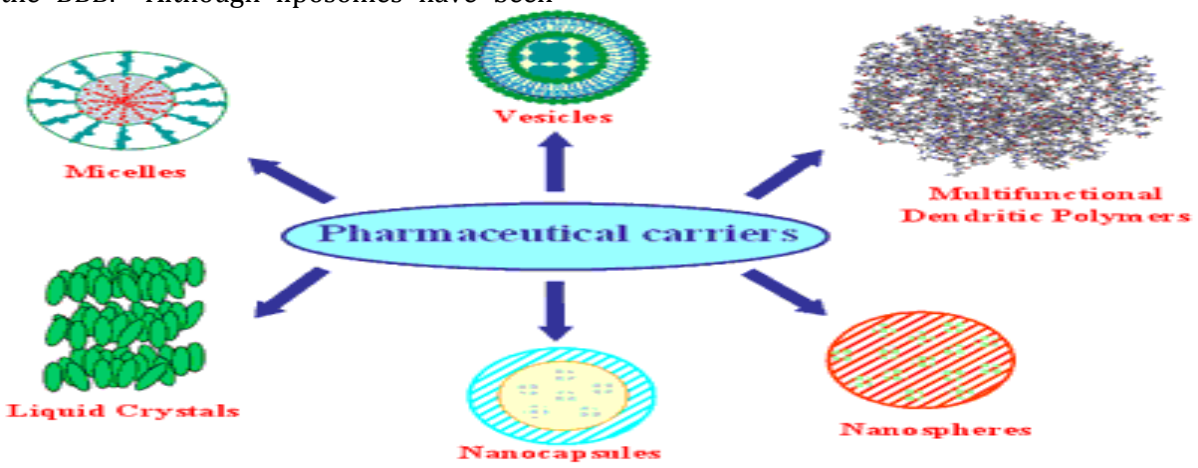

Fig. 5: Schematic representation of the different Pharmaceutical carriers for drug penetration across the BBB.

Nanoparticles

Nanoparticles (NPs) are solid colloidal particles made up of polymeric materials ranging in size from 1-1000 nm. This definition includes both nanocapsules, with a core-shell structure (a reservoir system), and nanospheres (a matrix system). NPs are used as a carrier systems in which the drug is dissolved, entrapped, encapsulated, adsorbed or chemically linked to the surface [30].

NPs possess the advantage of a high drug loading capacity and can provide protection against chemical and enzymatic degradation. Examples of synthetic polymers used to prepare NPs are poly (alkylcyanoacrylate) (PACA), acrylic copolymers, poly(D,L-lactide-co-glycolide), and poly(lactide). NPs have also been prepared from natural proteins (albumin and gelatin) and polysaccharides, starch and chitosan).

Like liposomes, NPs are rapidly cleared from the blood following intravenous administration. As carriers for drug delivery to the brain, NPs need to be small (<100 nm) to avoid the RES, neutrophil activation, platelet aggregation, and inflammation.

Besides solid polymeric nanoparticles (NPs), solid lipid nanoparticles (SLN) have also been employed for delivering drugs to the CNS.

SLN are dispersions of solid lipids stabilized with emulsifier or emulsifier/co-emulsifier complex in water.

In particular, delivery to the brain of antitumor drugs, including camptothecin, doxorubicin and paclitaxel, incorporated into SLNs and PEGylated SLNs is studied [31-32].

In all of the studies it has been found that significantly higher drug concentrations is detected in the brain when the antitumor drug is encapsulated and delivered in a SLN. It is therefore a noteworthy finding that SLNs appear by their nature to be capable of overcoming the BBB.In comparison with surfactant coated polymeric NPs (specifically useful in bypassing BBB), SLN have also been evaluated for brain delivery of the potent and frequently used HIV protease inhibitor (PI), atazanavir, that, like other PIs exhibits low brain permeability [33].

Polymeric Micelles and Microemulsions-

Polymeric micelles as drug delivery systems are formed by amphiphilic copolymers having an A-B dib lock structure with A, the hydrophilic (shell) and B, the hydrophobic (core) polymers. The polymeric micelles are thermodynamically and kinetically stable in aqueous media.

The size of polymeric micelles usually varies from ca. 10 to 100 nm. This narrow size range is similar to that of viruses and lipoproteins.

The core is composed of hydrophobic polymer blocks [e.g., poly (propylene glycol) (PPG), poly (D, L-lactide), poly (caprolactone), etc.] and a shell of hydrophilic polymer blocks (e.g., PEG). Most of them are biodegradable and biocompatible.

Earlier studies have shown that poloxamer (PluronicTM) micelles conjugated with antibodies may improve brain distribution of haloperidol, a neuroleptic agent. This approach resulted in a dramatic improvement of drugefficacy. This result indicates that Bio conjugates, Biomimetic polymers provide an effective transport of solubilized neuroleptic agents across the BBB [34-36].

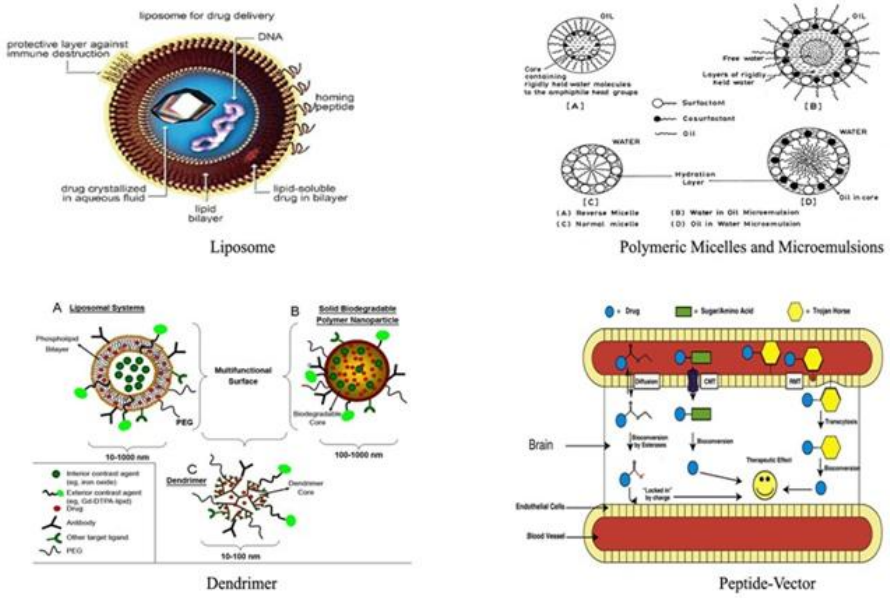

Fig. 6: Schematic representation of the different Pharmaceutical carriers for drug penetration across the BBB.

Dendrimers

Dendrimer is a highly branched polymer molecule formed by a central core to which the branches are attached, the shell of the branches surrounding the core, and the surface formed by the branches termini. They are of small size comparable to that of polymeric micelles or nanoparticles of small dimensions. Thus, for instance, a typical dendrimer molecule, such as poly(amidoamine) (PAMAM) dendrimer,has a diameter ranging from 1.5 to 14.5 nm.

As carriers for drug delivery to the brain, dendrimers conjugates with anti-cancer agents have been studied for the treatment of tumors at CNS level. In addition, gene delivery into brain has been also shown

using a transferrinconjugated PEGmodified PAMAM dendrimer [37].

Peptide-Vector-Mediated Strategy

The other approach for the delivery of neuropharmaceuticals is the use of small naturally derived peptides that cross cellular membranes efficiently, for example, pegelin and penetratin peptides (18 and 16 amino acids, respectively). SynB1 and pegelin (RGGRLSYSRRRFSTSTGR; molecular mass 2099 Da) is derived from natural peptides called protegrins. They have an amphipathic structure in which the positively charged and hydrophobic residues are separated in the sequence. Replacement of the four cysteine residues with serine residues leads to linear peptides (pegelin). The potential of this approach as an effective delivery system for transporting drugs across the BBB has been demonstrated in animal models [38].

Novel Methods

The challenging domain of effective brain delivery has led to a keen scientific pursuit and as a result many novel methods have been invented and patented. In these series, researchers have revealed the use of iontophoresis as an adjuvant for CNS drug delivery. Iontophoresis has been defined as the active introduction of ionised molecules into tissues by means of an electric current. The parent US patent method and device for delivery of a biologically active agent that is transported by means of iontophoresis and/or phonophoresis directly to the CNS using the olfactory pathway to the brain and thereby circum-venting the BBB and is known as transnasal iontophoretic delivery [39].

Molecular Trojan Horses

Endogenous ligands for specific BBB receptors, also known as Trojan horses, have the capacity to shuttle drugs into the brain.Vasoactive intestinal polypeptide (VIP) participates in the regulation of cerebral blood flow; however, in vivo studies showed no neuropharmacological effect as a result of low transport of peptide to the brain, which is attributable to the presence of the BBB.

CONCLUSION

From the above discussion it is found that many delivery systems like polymeric Nanoparticles and liposomes are the promising carriers to deliver drugs beyond the BBB for the scrutiny of the central nervous system. This is even more evident in light of the fact that most of the potentially available drugs for CNS therapies are large hydrophilic molecules, e.g., peptides, proteins and oligonucleotides that do not cross the BBB. Among the several strategies attempted in order to overcome this problem, properly tailored NPs may have a great potential.

The large amount of evidence regarding brain drug delivery by means of P80-coated NPs cannot be ignored or considered as single evidence even though its action mechanism is not completely understood. Lipid NPs, e.g. SLN, NLC, LDC NPs, may represent, in fact, promising carriers since their prevalence over other formulations in terms of toxicity, production feasibility and scalability is widely documented in the literature. The ability of engineered liposomes to enter into brain tumors makes them potential delivery systems for brain targeting.

A technology of chimeric peptides which are potential BBB transport vectors and have been applied to several peptide pharmaceuticals, nucleic acid therapeutics, and small molecules to make them CNS transportable.

It is estimated that the global CNS pharmaceutical market would have to grow by more than 500% just to equal the cardiovascular market.

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