RECENT ADVANCES IN BRAIN TARGETED DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Drug delivery to the Central Nervous System (CNS) in treatment of CNS related disorders is very complicated and challenging. Although some neuropharmaceutical agents have great potential for treating CNS disorders, major challenge to CNS drug delivery is the Blood Brain Barrier (BBB), which hinder the access of drugs to the brain. Progress in brain drug delivery has lagged behind other areas because of the restrictions posed by the BBB. This review encompasses detailed discussion of some of the recent drug delivery systems like Dendrimers, Polyanhydrides, Lipoplexes, Polyplexes, Scaffolds, Convection-enhanced delivery, and Modified nanoparticles for targeting drugs to the brain.

Keywords: Blood Brain Barrier, Dendrimers, Polyanhydrides, Lipoplexes, Polyplexes, Scaffolds, Convection-enhanced delivery, Modified nanoparticles.

INTRODUCTION

Drug delivery to the Central Nervous System (CNS) in treatment of CNS-related disorders is very complicated and challenging.

Drugs can be administered directly into the CNS or administered systemically for targeted action. Although some neuropharmaceutical agents have great potential for treating CNS disorders, major challenge to CNS drug delivery is the Blood Brain Barrier (BBB), which hinders the access of drugs to the brain.

Progress in brain drug delivery has lagged behind other areas because of the BBB. Advanced techniques and technological developments have helped in understanding of the cell biology of the BBB and thus have created newer ways for improved drug delivery to the CNS. The current challenge is to develop drug delivery strategies that will allow the passage of drug through the BBB in a safe and effective way. This review encompasses detailed discussion of some of the recent drug delivery systems for targeting drugs to the brain.

Fluid brain barriers

1. The BBB associated with capillaries, venules, arterioles, non-fenestrated endothelia of cerebral blood vessels
2. The Blood-Cerebro Spinal Fluid barrier associated with epithelia of the choroid plexus
3. The Blood-Nose barrier associated with epithelia of the nasal mucosa
4. The Arachnoid matter-Cerebro Spinal Fluid barrier

BBB shows close proximity of paracrine type of interactions between cerebral endothelial cells, pericytes, astrocytes, microglia and neurons. Anatomically, BBB is a continuous zipper-like tight junction of endothelial cellular layer. The microvascular endothelium shares a common basement membrane with astrocytes and pericytes. Astrocytes give out their foot processes to invest more than 90% of endothelial capillaries. In the capillaries, the ratio between pericytes and endothelial cells is approximately 1:2. The endothelial layer can be assumed to have two separate membranes, one on the inside of the vessels (luminal) and other to be the outside (abluminal).

These two membranes are separated by 300-500 nm thick layer of cytoplasm. The endothelial cells express numerous functional proteins that are involved in various transports, receptor-signal transduction and cell-mediated mechanisms. Peptides involved in the control of BBB related transport mechanisms, are secreted by astrocytes and neural endings and are either active in paracrine fashion on the abluminal side of the BBB or may originate from circulating blood, acting on the luminal side of the BBB. The tight junctions exclude paracellular pathway and show absence of pinocytosis across capillary endothelium. Tight junctions provide significant transendothelial electrical resistance (TEER) and impede the penetration of potential therapeutic agents such as oligonucleosides, antibodies, peptides and proteins.

Fig. 1: Fluid brain barriers [1]

Fig. 2: Cell biology and anatomy of BBB [3]
RECENT ADVANCES IN BRAIN TARGETING

Dendrimers The term dendrimer is derived from Greek words “Dendron” meaning trees or branches and “meros” meaning part. Dendrimers are strong bases and have highly predictable number of positively charged surface groups. The components of dendrimers

- Initiator core
- Interior layers (composed of radially attached repeating units to initiator core)
- Exterior attached to the outermost interior layer

In large dendrimers, all the bonds converge to the central core unit as a result of which they adopt globular shape. Dendrimers used in targeted drug delivery are usually 10-100 nm. Dendrimers start from a core molecule with at least three chemically reactive arms. To these arms, multiple branches are attached. As the density of branches increases, the outermost branches arrange themselves in the form of sphere surrounding a lower density core. At higher generations, dendrimers resemble spheres, with a number of cavities within its branches which hold both drug and diagnostic agents. Dendrimers with hydrophobic surface groups are lipophilic in nature. Dendrimers allow a large number of contrast agents to be introduced onto a single molecule, enhancing imaging sensitivity in medical imaging. Dendrimer based Magnetic Resonance Imaging (MRI) contrast agents provide greatly enhanced images of brain. The BBB possesses specific receptor-mediated transport mechanisms that can be exploited as a means to target drugs to the brain. Receptors expressed on the BBB, including Transferrin (Tf) receptor have been used for brain-targeting drug delivery research

Properties of dendrimers:
- Structural uniformity
- Monodispersibility
- Nanoscale size and shape
- Higher generation dendrimers can be considered as synthetic mimics of proteins
- Improve intracellular trafficking of drug [5]

Classification of dendrimers:
- Hybrid dendrimers (combination of dendritic and linear polymers in hybrid block)

E.g.: Poly (amidoamine) [PAMAM] dendrimers:

I. PAMAM dendrimers with primary amino surface groups have an inherent ability to associate with and condense DNA, and have been used for high efficiency DNA delivery. The primary amines located on the surface of PAMAM make it possible to conjugate suitable ligands, such as Tf, for efficient brain-targeting gene delivery. Tf was selected as the brain-targeting ligand conjugated to PAMAM via bifunctional polyethylene glycol (PEG), yielding PAMAM-PEG-Tf. This vector showed a concentration dependant manner in cellular uptake study and a 2.25 fold brain uptake compared with PAMAM and PAMAM-PEG alone. Transfection efficiency of PAMAM-PEG-Tf/DNA complex was much higher than PAMAM-PEG/DNA complex. With a PAMAM/DNA weight ratio of 10:1, the gene expression of PAMAM-PEG-Tf/DNA complex was two-fold higher than that of PAMAM/DNA and PAMAM-PEG/DNA complexes. These results suggested that PAMAM-PEG-Tf can be exploited as a potential non-viral gene vector targeting to brain via intravenous (IV) route of administration [6]

II. Transgeden® is a novel hybrid dendrimer having rigid polyphenylenvinylene (PPV) core with flexible polyamidoamine (PAMAM) branches at the surface. It is a non viral vector for siRNA delivery to the CNS. It was observed that dendrimers formed by Transgeden and siRNA had almost 100% incorporation efficiency in neuronal cells without toxicity [7]
**Simple dendrimers (simple monomer units)**

E.g.: Boronated starburst dendrimers:

Chemically bridging of fundamental building blocks of dendrimers leads to a new class of macromolecules, called as starburst polymers. This involves chemical reaction between dendrimers with nucleophilic surface and those with electrophilic surfaces, resulting in dendrimers with dramatically enhanced dimensions (also called as nanoscopic compounds, clusters and polymers).

\[ G_1 \rightarrow G_n \]

**Dendrimers Starburst polymer**

Boron neutron capture therapy is based on neutron capture reaction when 10-Boron \(^{10}\)B is irradiated with low energy to yield \(\alpha\)-particles and recoiling 7-Lithium \(^7\)Li nuclei. If monoclonal antibodies are to be used for targeting along with \(^{10}\)B, it is essential that they recognize a membrane epitope that is highly expressed on tumor cells. Boronated starburst dendrimers monoclonal antibody immunonconjugates are used for targeting primary and metastatic brain tumors.

**Other dendrimers for brain targeting:**

- Vivagel\(^{TM}\) is the first dendrimer that has been already entered into phase II human clinical trials. These are developed by Starpharma (Melbourne, Australia). Vivagel\(^{TM}\) binds to HIV glycoprotein-120 and has significant role in brain targeted treatment of HIV [4]. It is anionic functionalized poly (L-lysine) dendrimer. A G4 poly (L-lysine)-based dendrimer with naphthalene disulfonic acid surface groups (i.e. SPL7013) is the active ingredient in Vivagel\(^{TM}\) [8].

- Kannan et al. studied efficacy of systemically administered PAMAM dendrimers for treatment of cerebral palsy. They found that the dendrimers localized in activated microglia and astrocytes in the brain of newborn rabbits with cerebral palsy, but not healthy controls. It was found that dendrimer-based N-acetyl-L-cysteine therapy for brain injury suppressed neuroinflammation and leads to a marked improvement in condition [9].

**Polyanhydrides**

Polyanhydrides are bio-degradable polymers which release the drug mainly by simple hydrolysis. Polyanhydrides are basically intracerebral implants useful for controlled drug delivery. In Polyanhydrides, drug is embedded in polymer matrix [10]. They degrade uniformly into non-toxic metabolites that are non-inflammatory, non-mutagenic and non-cytotoxic. Their degradation profile can be modulated from days to months by varying the type and ratio of the monomers. Polyanhydrides are believed to predominantly undergo surface erosion due to:

- The high hydrophilicity of the anhydride bonds on the surface
- Hydrophobicity, which restricts water penetration into the bulk

A decrease in the device thickness throughout the erosion process, maintenance of the structural integrity and the nearly zero-order degradation kinetics suggest that the heterogeneous surface erosion is taking place. High hydrolytic reactivity of the anhydride linkage provides versatility and control of degradation [11]. The drug is slowly released from these for three to weeks to destroy any remnants of tumor. Because of the local delivery of the drug, harmful systemic side effects are avoided [12].

**Polyanhydrides in brain tumor:**

Brain tumor Glioblastoma multiforme (GBM) accounts for about 80% of adult primary brain tumors and are usually found in the cerebral hemispheres. Many of the anti-cancer drugs have large molecular structures, ionic charge or are hydrophilic and thus are unable to cross the BBR, and intolerably high systemic levels are required to achieve the therapeutic doses within the CNS.

Use of polyanhydrides for direct localized delivery is one of the simplest approaches.

- Gliadel\(^{®}\) wafers are approved by FDA in 1996. These are commercially available and one of the most successful delivery systems made of polyanhydrides. These are made up of Poly (CarboxyPhenoxy) Propane:Sebacic Acid, in the ratio of 20:80. These are dime-sized wafers that deliver BCNU (Carmustine), for the treatment of GBM. The wafers are directly placed in the resection cavity after tumor excision. After the debulking of the tumor, up to eight Gliadel\(^{®}\) wafers are implanted for the treatment along the walls of tumor cavity. It was found that Gliadel\(^{®}\) wafers release drug for about 5 days [11].

- Walter et al. have formulated polymeric disc of Poly (Carboxyphenox) Propane:Sebacic Acid, in the ratio of 20:80 with 20-40% of Taxol loading, and found that intact Taxol was released up to 1000 hrs, in vitro. They have reported that polyanhydride maintained concentration of 75–125 ng Taxol/ mg brain tissue, within a 1-3 mm radius of the disc and concluded that Taxol shows promising results in malignant glioma when delivered via the polyanhydride system [13].

- Local delivery of Minocycline for treatment of intracranial glioma is another application of polyanhydrides. Minocycline was incorporated in Poly (CarboxyPhenox) Propane:SebacicAcid) in a ratio of 50:50 by weight. It was found that combination of intracranial minocycline and systemic BCNU extended median survival by 82% [11].

**Lipoplexes and Polyplexes**

In order to improve the delivery of the new DNA into the cell, the DNA must be protected from damage and its entry into the cell must be facilitated. Lipoplexes and polyplexes serve this purpose. Both have the ability to protect the DNA from undesirable degradation during the transfection process. Plasmid DNA can be covered with lipids in an organized structure like a micelle or a liposome. When the organized structure is complexed with DNA it is called a lipoplex.

There are three types of lipids:

- Anionic (negatively charged)
- Neutral
- Cationic (positively charged)
Initially, anionic and neutral lipids were used for production of lipoplexes for synthetic vectors. Lipoplexes are compatible with body fluids, there is a possibility of adapting them to be tissue specific and there is very little toxicity associated with them. The only disadvantage is that they are complicated and time consuming to produce.

Thus, attention was turned to the cationic versions. Cationic lipids, because of the positive charge on them, have ability to naturally complex with the negatively charged DNA. Also because of the positive charge, they interact with cell membrane, endocytosis of the lipoplex occurs and the DNA is released into the cytoplasm. The cationic lipids also protect against degradation of the DNA by the cell. Cationic lipids include Diocetyl phosphoethanolamine (DOPE), dioleyl trimethylammonium chloride (DOTMA) [14], Sawant et al. formulated TATp (TAT polymers) lipoplexes with cationic lipid N-[1-(2,3-Dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl-sulfate (DOTAP). The lipoplexes showed higher transfection efficiency in vitro when incubated with mouse fibroblast [15].

Complexes of polymers with DNA are called polyplexes. Most polyplexes consist of cationic polymers and they are formed by ionic interactions. One large difference between the methods of action of lipoplexes and polyplexes is that polyplexes cannot release the associated DNA into the cytoplasm. For release to take place co-transfection with endosome-lytic agents which lyse the endosome must occur and the polyplex enters the cell. However this is not always the case, polymers such as Polyethyleneimine (PEI), chitosan and trimethyl chitosan have their own method of endosome disruption. PEI forms dense nanosized particulates and complexes with negatively charged DNA by electrostatic interactions. The PEI/DNA complex takes overall positive charge and interacts with negatively charged components of cell membranes and enter cells by endocytosis. The PEI/DNA complex enters the cells by non-specific adsorption mediated endocytosis. Upon endocytosis, PEI undergoes further protonation as the endosomal compartment acidifies. Protonation of PEI occurs by capturing protons, which is called as Proton Sponge mechanism. This leads to osmotic swelling and subsequent endosomal disruption. Zhanta et al. demonstrated that only one nuclear localization signal (NLS) peptide covalently linked to DNA could increase the transfection efficacy following an intracranial injection of the plasmid [16]

c) Scaffolds [17]

Scaffolds are implantable and can be used to treat a variety of conditions associated with brain injury and diseases, for delivering drugs to treat neurological diseases such as Parkinson’s disease and Alzheimer’s disease. Delivery of therapeutic agents from scaffolds potentially helps to limit the damage to neurons while helping to preserve their function.

Although scaffolds have wide range of potential applications for neural tissue engineering, the brain presents similar obstacles when designing scaffolds. Considerations include:

- Minimizing cell death and inflammation after implantation of scaffolds, by choosing biocompatible materials
- Controlling drug release over an appropriate time period to prevent multiple surgeries or injections
- Making the whole process minimally invasive to preserve the integrity of the BBB
- Scaffolds should be small and minimally invasive

**Table 1: Types of scaffold materials used in nerve disorders**

<table>
<thead>
<tr>
<th>Types of nerve disorders</th>
<th>Natural Materials</th>
<th>Synthetic Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential scaffold materials for neuro-degenerative diseases</td>
<td>Agrose, Alginate</td>
<td>Poly (lactic acid) [PLA], Poly (glycolic acid) [PGA], Poly (lactic glycolic acid) [PLGA], Ethylene-vinyl acetate co-polymer [EVAC]</td>
</tr>
<tr>
<td>Potential scaffold materials for peripheral nerve injury</td>
<td>Collagen, Dextran, Hyaluronan, Hyaluronic acid</td>
<td>Poly (ethylene glycol) [PEG], Poly (ethylene oxide) [PEO], Poly (2-hydroxyethyl methacrylate) [PHEMA], poly (2-hydroxyethyl methacrylate-co-methyl methacrylate) [PHEMA-MMA]</td>
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**Scaffolds for brain drug delivery**

- Woerly S et al. studied efficacy of poly (hydroxyl phenyl methacrylate) [PHMPA] and PHEMA scaffolds containing glucosamine or N-acetylglucosamine groups when implanted between the septum and the hippocampus in a limbria-fornix lesion cavity. It was found that PHEMA scaffolds showed markedly less infiltration of connective tissue than PHMPA [18]

**d) Convection-enhanced delivery [19]**

Intraoperative injection of anti-cancer agents into brain tumors has limited success due to diffusion-limited drug distribution as well as leakage away from the target site. Convection-enhanced delivery (CED) is a type of direct administration that makes the use of positive pressure to increase circulation of drug throughout the tumor. CED is practiced either in acute infusions by attaching an implanted catheter to an external pump. For more prolonged infusions, catheters can be attached to implantable osmotic pumps. Using CED, high concentrations of drugs can be delivered in tumor tissue. Through careful stereotactic implantation of CED catheters, normal tissue can be spared. Poor cannula placement can result in leakage of drug away from the target site, potentially leading to adverse effects, such as chemical meningitis. The highly variable intracranial distribution of glioma tumors is the additional challenge for the use of CED as it requires an individualized cannula placement plan for each patient. Optimal cannula placement can be aided by the FDA-approved software iPlan by BrainLAB, which models fluid flow in the brain and provides feedback regarding cannula location. iPlan algorithms are rapidly evolving to assist in more accurate cannula placements and more thorough drug distribution.

**Protein delivery by CED:**

Due to high molecular weight, therapeutic proteins are common candidates for CED. Most therapeutic proteins investigated for the treatment of malignant glioma consist of a cytotoxic moiety, often a bacterial toxin, combined with a targeting moiety for selective therapeutic effect on glioma cells. Cytotoxic moiety is derived from Pseudomonas aeruginosa exotoxin (PE). Other notable fusion proteins being investigated for efficacy by CED include, TransMD-107 (TF-CRM107). TransMD-107 is a diptheria exotoxin fused to TF and binds to the TF receptor, which is commonly over expressed in malignant glioma. The safety of TransMD-107 has been demonstrated in Phase I and Phase II studies of clinical trials.

**CED of oligonucleotides and liposomes:**

CED is the delivery method of choice for large molecules and biologics, such as oligonucleotides, drug bearing liposomes and viral mediated therapies. Trauberssen [AP-12009] is an antisense oligonucleotide that targets the transcript for Transforming Growth Factor-beta2 (TGF-β2), a protein involved in tumor growth and survival. Liposomal drug carriers encapsulate small molecule chemotherapeutics and can improve the pharmacokinetic profile of these agents by reducing drug clearance time. When delivered by CED, liposomal agents achieve acceptable tumor coverage, as indicated by MRI using gadolinium-loaded liposomes. Irinotecan has shown impressive efficacy in preclinical studies when delivered by CED. Tumor cells responded with a 15-30% reduction in proliferation.

Liposomal Irinotecan decreased tumor vascular density. Though of tremendous potential to improving clinical outcomes for malignant
glioma patients, CED faces several challenges for achieving more widespread use:

I. Highly variable nature of CED-associated therapeutic distribution in tumors
II. Procedure is highly invasive
III. Limitations in the number of dosing cycles
e) Modified nanoparticles:
The utilization of the nanoparticles as a vector for brain drug delivery has the following advantages:

- Excellent engineerability
- Non-toxicity
- Controllable loading/releasing of active agents (drugs/contrast agents)
- Targeted nanoparticles can achieve the delivery of large amounts of therapeutic or imaging agents
- The nanoparticles with enhanced surface properties (targeting and/or hydrophilic coating) may be able to deliver a high amount of drugs/contrast agents selectively to tumor sites and improve the efficacy of existing imaging and treatment of cancer in general

The exact mechanism of nanoparticle transport into the brain is most likely:

- Receptor-mediated endocytosis
- Phagocytosis
- Passive leakage across defects in the BBB

Types of nanoparticles

1. Multifunctional nanoparticles [20]

Multifunctional nanoparticles are 20-200 nm diameter nanoparticles. These are also called as Probes Encapsulated by Biologically Localized Embedding (PEBBLEs). Their components include:

- A targeting agent that directs the particle to cancer cells
- A protective coating (PEG) that helps it cross the BBB
- Photodynamic molecules that catalyze the conversion of oxygen to highly reactive oxygen singlet
- Magnetically dense metals for MRI contrast imaging
- Fluorescent “beacon” to visually pinpoint the nanoparticles location

The major potential advantage of using PEBBLEs to treat cancer is their multifunctionality.

- One target molecule immobilized on the surface could guide the PEBBLE to a tumor
- Another agent could be used to help visualize the target using MRI

MRI contrast element: Gadolinium

- Third agent attached to the PEBBLE could deliver a destructive dose of drug or toxin to nearby cancer cells

All three functions can be combined in a single tiny polymer sphere to make a potent therapeutic system against cancer. When injected into the bloodstream, the nanoparticles travel through the bloodstream. As they can transverse the BBB and have a targeting agent attached, the PEBBLEs accumulate in the brain tumor enabling a clear MRI image within just a few hours. Each PEBBLE carries a photocatalyst. When stimulated by a light source through a micrometer-sized fiber optic probe inserted into the skull, the photocatalyst converts oxygen into singlet state, which effectively bleaches and destroys nearby cells. The PEBBLEs are inert and harmless until the light is turned on. Used in combination with MRI imaging, cancer cells can be killed along with tracking the effectiveness of the treatment with imaging. The targeted treatments using PEBBLEs has a number of advantages over traditional chemotherapy.

As PEBBLEs are highly localized to the cancer target, very little damage is caused to surrounding healthy tissue. PEBBLEs act on the outside of the cell and the toxic oxygen which is delivered by them acts quickly, without giving the cancer cells chance to survive and develop resistance. In this way, they overcome multiple drug resistance. In the most common form of primary brain cancer is glioblastoma, surgery has limited effectiveness because of difficulty in visually differentiating cancer cells and normal brain tissue and any cancer cells left behind are likely to proliferate and form new tumors. Thus, Fluorophores, i.e. glowing molecules were developed which mark the tumor boundaries and facilitate detection and removal of tumors.

Veiseh et al. formulated magnetic nanoparticles which had following components

- 10 nm diameter iron oxide core which serves as an MRI contrast material
- PEG coat at the surface
- Fluorescent molecule called Cy5.5 which gives off light at near infrared (IR) wavelengths, which can penetrate several centimeters through brain tissue
• Targeting agent Chlorotoxin, a peptide derived from the venom of the Giant Israeli Scorpion, which binds specifically to a tumor surface marker found in the majority of glioma. It selectively light up glioma tumors

It was observed that at 15 nM, the final particle size and composition resulted in crossing the BBB to a sufficient extent [21]

2. Magnetic nanoparticles for MRI:

MRI of the CNS is usually performed with short-lived Gadolinium-based contrast agents. Iron oxide nanoparticle-based MRI contrast agents show excellent potential for the CNS imaging. The iron oxide contrast agents are known as super-paramagnetic iron oxide (SPIO) or ultra small super-paramagnetic iron oxide (USPIO) agents, depending on the size distribution of the nanoparticles. Some of the SPIO and USPIO are already clinically approved or on preclinical trial.

Two generic types of magnetic nanoparticles have been used:

• Iron oxide core surface-coated with polymer:

Dextran-coated USPIO have been investigated by in vitro cellular studies and in vivo animal studies as well as human studies for evaluating their efficacy as MRI contrast agents in the brain. The USPIO consist of a 5-6 nm iron oxide core surrounded by a dextran coating. Their hydrodynamic diameter is about 20-30 nm.

I. The in vitro cellular uptake studies were performed in tumor cells with 125I-labeled or fluorescently labeled dextran-coated iron oxide nanoparticles. The cellular uptake was found to be varying but ubiquitous in different tumor cells and was not saturable. This suggested that their transport mechanism was fluid-phase endocytosis.

II. The in vivo animal studies were performed on rats implanted with gliosarcoma. MRI was performed 14 days after tumor implantation. Images were taken before and 24 hours after injection of dextran-coated iron oxide nanoparticles containing 19 mg/kg iron. All the images were obtained with a 1.5-T superconducting magnet. It was found that total amount of nanoparticles taken up by the gloma was sufficient to alter the MRI signal intensity at tumors, compared to that at adjacent brain tissues.

III. An in vivo bio-distribution study with 125I-labeled dextran-coated iron oxide nanoparticles was conducted which showed that 24 hrs after IV administration, accumulation in brain tumor was low (0.11% of injected dose) but was 10-fold higher than healthy brain tissue adjacent to the tumor. The pattern of distribution of the iron oxide nanoparticles in tumor was studied which showed that the nanoparticles accumulated preferentially in the periphery of the tumor and heterogeneously throughout the remainder of the tumor.

These agents can be used for both intraoperative and post-operative imaging of residual tumor as they have long plasma half-life (24-30 hours). USPIO nanoparticles leak across the breached BBB, get trapped intracellularly by astrocytes, macrophages in and around the tumor which leads to MRI enhancement.

• Nanoparticles with incorporated iron oxide:

These nanoparticles are prepared by incorporating iron oxide crystals into polymer matrices. These are bigger than the conventional iron oxide nanoparticles.

I. The polyacrylamide nanoparticles with encapsulated super-paramagnetic iron oxide crystals were used for in vivo MRI of brain tumor in a rat gliosarcoma model. The nanoparticles with or without surface-linked PEG of different sizes were prepared. The results showed that each of these nanoparticles encapsulated many iron oxide crystals into the polyacrylamide matrix and resulted in a stable nanoparticle.

II. The in vivo pharmacokinetic studies were performed with four different nanoparticle preparations (one non-PEGylated and three PEGylated iron oxide-encapsulated polyacrylamide nanoparticles) on rats bearing gliosarcoma. The results reveal significant MRI contrast in the tumor mass as compared to the normal brain for all nanoparticle preparations. The higher degree of contrast enhancement that was found in the tumor periphery, compared with the tumor core, because of the higher vascular density across the periphery. Changes in vasculature MRI signal intensities showed that the plasma half-life increased with the size of the PEG subunits.

The mechanism of the accumulation of these nanoparticles in the brain tumor includes:

• Diffusion/convection through the altered/disrupted BBB
• Interaction of PEG with the brain endothelial cells

The nanoparticles with incorporated iron oxide can be potent MRI contrast agents with enhanced brain uptake, as compared to polymer-coated SPIOs for brain cancer [22]

CONCLUSION

Delivering drugs effectively for treatment of CNS-related disorders is impeded by lack of specific and efficacious approaches. Despite these obstacles, significant progress has been made in the strategies for brain targeting. But none has been proved to be satisfactory.

The present drug delivery strategies from point of view of patients suffering from CNS-related diseases remain poor, but recent developments in drug delivery across the BBB have proven to be helpful for overcoming barriers associated with brain drug delivery. Nanotechnology and various other delivery systems can be further explored for their great potential in penetrating the BBB efficiently.

Lack of training to brain drug targeting specialists and lack of prominence in pharmaceutical industries are some of the obstacles in future progress in this area. Future developments include identification of new BBB transporters, application of genomics and proteomics and stem cell therapy and emphasizing on development of novel imaging agents. This area requires innovative approach and constant research.

REFERENCES