The treatment of brain cancer is still a biggest challenge for oncologists due to the presence of blood-brain barrier (BBB). BBB protects the brain by restricting the entry of different substances in the brain from the body; simultaneously prevent the passage of drug molecules from the blood to the tumor site inside the brain during chemotherapy. With the use of nanotechnology, the said problem can be resolved and therefore it attracts nanotechnologists towards the development of nanocarriers. The nanocarrier's especially solid lipid nanoparticles (SLNs) have a characteristic to pass through the BBB. This characteristic makes these nanoparticles as an excellent tumor targeting carrier. The SLNs can target the blood brain barrier by means of various targeting options i.e. carbohydrates, proteins, vitamins, amino acids etc. SLNs also enhance the cellular uptake of various encapsulated cytotoxic drugs. This review article summarizes the various targeting options currently used by various researchers to target the BBB by the use of SLNs for the treatment of brain cancer.

1. INTRODUCTION

Brain cancer is the main cause of death among the deaths related to cancer in children under age of 20 just in America. According to brain tumor association, in the U.S only 700,000 people are living with a primary brain and central nervous system tumor. In the year 2017, nearly 17,000 people lost their battle of life with a primary brain and central nervous system cancer (www.abta.org.). This is because, the treatment of such diseases are still the biggest challenge in oncology due to the presence of blood-brain barrier (BBB) which limits the entry of drug molecules to reach the tumor sites. Also, the systemic administration of most of the anticancerous drugs causes severe side effects. Therefore, considerable efforts have been made by various researchers to develop novel targeted delivery systems that have high selectivity to cancer cells with no/minimal effect on normal cells. Among them liposomes, niosomes, microspheres, cyclodextrins, dendrimers, nanoparticles etc. has been developed and investigated in different experimental models.

Overview on the current brain cancer treatments

The brain cancer is usually treated by surgery, followed by radiation, and chemotherapy. The main aim of the surgery is to remove most of the cancer cells without injuring any adjacent normal brain cells. But it is difficult to remove the entire mass of tumor because tumor cells are surrounded by migrating as well as infiltrating tumor cells that invades the surrounding tissues.

Surgery is followed by radiation, and chemotherapy. Radiation therapy kills the remaining tumor cells which have not been removed by the surgery. In the radiation therapy, standard-dose "fractions" of radiations are delivered to the tumor site as well as in margins to treat the zone of infiltrating tumor cells. Each treatment involves damage to both unhealthy and normal cells.

Chemotherapy involves the administration of cytotoxic drugs that are based on a patient's overall health, type of tumor, and the extent of cancer. As compared to radiation, chemotherapy treats cancer on a cellular basis in all over the body. Therefore, it is considered as a systematic treatment. Chemotherapy helps to treat cancer effectively and thus it also enhances the quality of life of patients diagnosed with cancer. But there are chances of remission of tumors even after surgery, radiation and chemotherapy and therefore researchers are continuously formulate and investigate the new nanocarriers for the effective cancer treatment.
A number of these novel treatments, utilizing nanotechnology are available on an investigational basis at centers specializing in brain cancer treatment.

Problems in conventional treatment of brain cancer and BBB

Brain cancer is different from other type of cancers because of the existence of the “blood-brain barrier”. BBB mainly consists of endothelial cells, astrocytes, and pericytes cells (Fig. 1). BBB protect the brain from the danger by restricting the entry of different substances in the brain from the body. At the same time it creates the problem during chemotherapy of brain cancer. According to Dr. Robert Burdick, oncologist and professor at the University of Washington Medical School "As a rough estimate, neurosurgeons do well to cure one in every 1,000-brain cancer patients they operate on. Radiation therapy slows the growth of adult tumors, gaining perhaps one month of life, and may result in a cure of only one in 500-1,000 patients. Similarly, chemotherapy, despite 30 years of clinical trials, has not resulted in the development of a single drug or drug combination that elicits more than an occasional transient response in primary brain tumors." Also conventional administration of different cytotoxic drugs, leads their binding to different tissues and plasma proteins results wide biodistribution which is undesirable. As a result, only a small amount of cytotoxic drugs reached to the cancer cells. Moreover, the binding ability of cytotoxic drugs with cancer tissues is always very poor which is considered as a major challenge for the effective treatment of cancer. Additionally various nonspecific and specific adverse effects are also associated with the use of cytotoxic drugs which are dose dependent. Nausea, vomiting, severe anemia, hair loss, and fatigue are the common adverse effects associated with most cytotoxic drugs. Also some cytotoxic drugs induce their own adverse effects on certain specific tissues or organs. Like doxorubicin induces cardiotoxicity, cisplatin causes nephotoxicity, and bleomycin leads to toxicity of lungs. Apart from BBB, multidrug resistance (MDR) also affects the chemotherapeutic treatment. MDR involves the active efflux of cytotoxic drug molecules from the cytoplasm via membrane bound transporters. Conclusively, the major troubles in conventional anticancer chemotherapy are the poor selectivity, high toxicity, and susceptibility to induce drug resistance. To overcome all these obstacles significant work have been done by the scientists to develop novel targeted drug delivery systems that are able to cross BBB as well as provide good selectivity to cancer cells with no or negligible effect on normal cells.

Solid lipid nanoparticles (SLNs) as delivery carrier for cytotoxic drugs

SLNs are one of the well characterized lipid-based nanocarriers used in the delivery of cytotoxic drugs for the treatment of brain cancer. These lipidic nanoparticles are emerging as a safer and efficient carrier for the delivery of cytotoxic drugs. SLNs are the submicron colloidal carriers of size range in between 50 nm to 1 µm, prepared mainly by high-pressure homogenization, ultrasonication, solvent evaporation, solvent emulsification–diffusion method and micro-emulsion based method from the solid physiologic lipids. SLNs can cross the BBB but the exact mechanism by which they cross is unknown. It is hypothesized that the internalization of these nanocarriers is mediated through endocytosis by endothelial cells of the BBBs.

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The SLNs target the BBB by means of various targeting options i.e. carbohydrates, proteins, vitamins, amino acids etc. The systemic administration of SLNs leads to their RES uptake includes opsonization of nanoparticles, phagocytosis by macrophages, and uptake in the liver and spleen. The RES uptake of the SLNs can be partially blocked by the attachment of hydrophilic moieties like polyethylene glycol, polysorbates (tweens) etc. to their surface.
Advantages of SLNs

SLNs offer many beneficial attributes in comparison to other colloidal drug delivery systems. These are:

- These are biocompatible carriers because of the physiological lipids and biocompatible surfactants by which they are made.
- They offer significant drug loading capability. Under optimized conditions, they are able to carry both lipophilic and hydrophilic moieties.
- Their colloidal dimensions allow their administration both by parenteral and non-parenteral routes.
- The RES uptake can easily be avoided with SLNs because of their small size i.e. 120–200nm.
- Controlled drug release from these nanocarriers can be made to last several weeks.
- They have high BBB permeability which makes them a suitable carrier for the drugs targeted to the brain.
- These could be easily produced and sterilized on industrial scale.

Drawbacks of SLNs:

The major drawbacks of SLNs are:

- Drug loading is limited by the solubility of drug in the melted lipid.
- Expulsion of drug during storage is due to formation of crystalline lattices by some lipids.

Various SLNs based targeted approaches for the treatment of brain cancer

SLNs are made up of biocompatible lipids and natural surfactants that made them an alternative carrier to the polymeric nanoparticles. Size up to 200nm, neutral surface charge, spherical shape, and sufficient deformability ensures their low RES uptake and prolonged blood circulation. SLNs have also been targeted specifically to the cancer cells by the grafting of various recognition moieties on their surface. In this review, the various approaches have been used to target the SLNs to brain cancer cells are discussed.

Plain SLN

SLNs will act as a promising vehicle for the delivery of various cytotoxic drugs to the cancer cells in the brain. This was proved by the work of many researchers encapsulated cytotoxic drugs i.e. idarubicin, paclitaxel, etoposide, edelfosine, camptothecin, doxorubicin in SLNs. SLNs improve the pharmacokinetic distribution of doxorubicin after i.v. administration in comparison to commercial doxorubicin solution. An unexpected appearance of doxorubicin was found inside the brain, which does not occur after administration of doxorubicin solution. Low drug concentration was reached in the liver, kidneys, and heart. The less uptake of doxorubicin loaded SLNs by the RES results its high bioavailability in non-RES tissue. The presence of stealth agents or pegylation of lipophilic surface of SLNs also increases their circulation in plasma and consequently helps their brain uptake. The stealth SLNs has been delivered the high drug concentration in the rat brain than non-stealth SLNs after i.v. administration. The uptake of drug by the brain varies with the amount of stealth agent on the SLNs. The amount of drug in the brain was increased with the increase in amount of stealth agent. The presence of PEG chains on the surface of the SLNs increases their hydrophilicity and subsequently resulted high circulation time. This could also allow the SLNs to cross the BBB in greater extent.

The various solid lipid nanocarriers used in the delivery of cytotoxic drugs with plain and functionalized SLNs in brain cancer therapy are summarized in Table 1. The positive charges on the surface of SLNs, not affect the brain uptake of drug significantly. Daniela et al noted no differences in cytotoxicity between neutral and charged SLNs.

Functionalized solid lipid nanoparticles

Targeted therapy for cancer treatment involves the targeting of genes, proteins, or the tissue environment which are very specific to tumor or tumor cells and responsible for cancer growth. This type of targeted delivery retards the growth and spread of tumor cells and also prevents the damage to healthy cells. Targeted therapy can be achieved by the functionalization of the nanocarriers. The endogenous transport systems used by the nanocarriers to cross the BBB are:

- Absorptive-mediated transcytosis (AMT)
- Transporter-mediated transcytosis
- Receptor-mediated transcytosis (RMT)

Functionalized SLNs have a potential for an active targeting. By exploiting different endogenous transport systems within the BBB, drugs are delivered to the brain. For this type of drug delivery, the systems are required to be altered like surface engineering of nanoparticles with ligands specific to brain cells. On the basis of this strategy various surface engineered SLNs are formulated, characterized, and evaluated for the brain cancer treatment. Various ligands conjugated to SLNs in the past years have been discussed in the following section.

Absorptive-mediated transcytosis

Absorptive-mediated transcytosis (AMT) provides a means for the delivery of drugs across the BBB by cationic proteins or cell-penetrating peptides (CPPs) e.g. protamine, poly-L-lysine, albumin, horseradish peroxidase. AMT is initiated by electrostatic interactions between the positively charged moieties of the proteins (basic isoelectric point) and negatively charged membrane of the brain endothelial cells.
AMT type CPP based delivery systems show great ability in BBB transport. CPPs has been used to cross the lipophilic barrier of cellular membranes and to deliver a large variety of molecules including peptide/proteins, DNA/oligonucleotide, antibodies, imaging agents, toxins, and nano drug carriers such as liposomes and micelles. CPPs are heterogeneous in size and sequence, and are positively charged. The CPPs are always derived from natural proteins including the transcription-activating factor Tat, penetratin, and the Syn-B vectors, among which Tat might be the most frequently used.

**Albumin coupled SLN**

Cationic Bovine Serum Albumin (CBSA) has been used as a ligand for brain targeting. CBSA has high selectivity for brain tissues than other body organs. CBSA engineered SLNs have been used to transport metothrexate across the BBB. Transport of fluorescent probes, across the BBB has been enhanced by CBSA via AMT. Transcytosis of CBSA engineered SLNs have been found to be more than unconjugated SLNs in in vitro cell line studies on brain capillary endothelial cells (BCs) and on human neuroglial culture (HNGC)-1 tumor cells.

**Transporter mediated transcytosis**

The different transport systems are present in cerebral endothelium that provides the necessary nutrients and endogenous substances to the brain. Near about 8 different transport systems have been identified e.g. carriers for large neutral amino acids (LAT1), cationic amino acids or organic cations, d-glucose (GLUT1), monocarboxylic acids (MCT1) etc. Each transport system has transport a group of nutrients with similar structures like glucose transporters (GLUT) facilitate the transport of d-glucose across the BBB, including 2-deoxyglucose, galactose, mannose, and glucose analogs. Mannose-modified liposomes were able to cross the BBB by utilizing glucose transporter with high affinity toward M6P receptor. Transporter mediated transcytosis takes advantage of these transport systems as a promising brain targeting strategy. Peptides and small molecules may use specific transporters present on the endothelial cells on both luminal and basolateral sides to cross the BBB. Another important transport system that is choline transporter binds positively charged quaternary ammonium groups or simple cations has also used successfully.

**Amino acid (Phenylalanine) coupled SLN**

Amino acids can transverse the BBB by specific carrier-mediated transporters. Specific L-Type amino acid transporters (LAT1) are over expressed on BBB as well as on many brain cancer cells. Thus the various amino acids can be used to target the brain cancer cells. Phenylalanine has been used to improve the anticancer activity of nanocarriers. Phenylalanine-coupled SLNs have been delivered the high amount of drug into the brain tumor cells. They showed high brain-targeting potential.

**Mannose derivative conjugated SLN**

Metabolic substrates like carbohydrates are also used to transverse the BBB by specific carrier-mediated transport systems like glucose transporters present on the both luminal and abluminal side of the BBB. P-aminophenyl-α-d-mannopyranoside (P-AM), a kind of mannose analog, has enhanced the brain delivery by the conjugation of SLNs. P-aminophenyl-α-d-mannopyranoside enhanced the cellular uptake of docetaxel loaded SLNs by the brain cells. Mannose-6-phosphate (M6P) is an oligosaccharide binds to the mannose-6-phosphate receptors (MPRs) which are type I transmembrane glycoproteins. The cation-independent mannose 6-phosphate receptor (CIM6PR) plays important roles in various biological processes. Its main role is transporting and sorting those lysosomal enzymes that contain an M6P-recognition marker in their structure from the trans-Golgi network to the lysosomes. CIM6PR also mediates the endocytosis of extracellular ligands such as insulin-like growth factor 2 (IGF2), retinoic acid and M6P-containing proteins.

**Betahydroxybutyric acid coupled SLN**

Betahydroxybutyric acid (HBA) is a ketone body and a substrate for the monocarboxylic acid transporter (MCT1) on the BBB. Transport of HBA across the brain is mediated by passive and/or carrier mediated diffusion. It has been also used as a ligand to transport the SLNs across the BBB. HBA enhanced the brain uptake of docetaxel loaded surface modified SLNs.

**Receptor mediated transcytosis (RMT)**

Generally, the specificity of the absorptive-mediated transcytosis as BBB targeting strategy is poor since the cationic proteins or CPPs can bind with any negatively charged cell membrane constituents. Also, the potential toxicity and immunogenicity of cationic proteins or CPPs limit their use. The transporter- mediated transcytosis is substrate selective and therefore drugs that closely mimic the endogenous carrier substrates will only be taken up and transported into the brain. RMT is considered one of the most mature strategies for brain targeted drug delivery with the characteristics of high specificity, selectivity and affinity; although the ligand may have an effect on homeostasis and natural ligands may compete with the drug ligand to reduce targeting efficiency. Different types of receptors are expressed on the capillary endothelium of the brain like transferrin receptors (TfR).
low density lipoprotein receptors (LDLR), insulin receptors and nicotinic acetylcholine receptors. Large molecules required for the normal brain function are delivered by these specific receptors. Targeting ligands, including endogenous ligands and ligands based on phage display or structure-guided design, have been exploited to facilitate receptor-mediated BBB transport of drug delivery systems.

The RMT has been completed in three steps, (1) Receptor-mediated endocytosis of the compound at the luminal (blood) side. (2) Movement through the cytoplasm of the endothelial cell. (3) Exocytosis of the drug at the abluminal (brain) side of the brain capillary endothelium. Transferrin receptors (TfR) are one of the most widely characterized receptor-mediated transcytosis systems for brain targeting. These receptors are highly expressed on endothelial cells of the BBB. Another common receptor, the low-density lipoprotein (LDL) receptor-related protein (LRP), has been reported to mediate transport of various ligands conjugated to nanocarriers across the BBB. Aprotinin is a LRP ligand and its BBB transport ability was evaluated using in vitro model of the BBB and in situ brain perfusion. Its transcytosis across bovine brain capillary endothelial cell monolayers was at least 10-fold greater than that of holo-transferrin. Angiopep, derived from aprotinin with the Kunitz domains of human proteins, exhibited even higher transcytosis capacity and parenchymal accumulation.

Nicotinic acetylcholine receptors (nAChRs) are a kind of ligand-gated ion channel that is widely expressed in the brain including the brain capillary endothelial cells. Since they bind the second loop of the three-finger snake toxin with high affinity and selectivity, nAChRs could be exploited to facilitate BBB crossing and intra cranial transport of drug delivery systems. By the receptor-mediated endocytosis, animal cells internalize many macromolecules. The process generally completed in three steps, (i) Cell surface binding (ii) internalization (iii) intracellular degradation. The process is initiated when receptors on the cell surface interacts with the macromolecules. After interaction, receptors binds with the macromolecules and slide laterally into clathrin-coated pits. The clathrin coated pits invaginate into the cell and pinch off to form coated endocytic vesicles. After shedding their clathrin coats and the vesicles fuse with one another to form endosomes. The ATP-driven proton pump acidifies the endosomes contents. Now from the endosomes, normally (but not always) the ligand is passed to lysosomes for degradation and the receptor cycles back to the cell surface to bind new ligand. It was observed that more than 25 specific receptors are participated in receptor-mediated endocytosis. These receptors include the transport proteins that deliver nutrients to cells (the cholesterol-carrying lipoprotein LDL, the iron transport protein transferrin, and the vitamin Bla transport protein transcobalamin II) and non transport plasma proteins (asialoglycoproteins, ~-2-macroglobulin, and immune complexes). In addition to it, the protein growth factors, like epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and polypeptide hormones like insulin and luteinizing hormone also enter cells by receptor-mediated endocytosis. The different pathways of receptor-mediated endocytosis are:

**Entry into coated pits**

In the receptor-mediated endocytosis all the receptors are moved into the coated pits. But the mechanism that triggers their movement into coated pits and the routes followed by the ligands and receptors after entering the cell was different. On that basis receptor-mediated endocytosis was divided into sub categories.

(i) This involves the receptors which spontaneously move into coated pits and enter cells continuously (even in the absence of ligand) e.g LDL, transferrin, ~-2-macroglobulin, asialoglycoproteins, and insulin.

(ii) This involves the receptors which wait on the surface until a ligand is bound, then after they are captured by coated pits e.g EGF

**Intracellular Routes**

After binding to ligands, it was found that all endocytic receptors enter cells in the same coated pits and then delivered to endosomes which are acidified due to ATP-driven proton pumps. After which receptor-ligand follows one of the route described below.

**Route 1: Receptor Recycles, Ligand Degraded**

In this route, due to acidic pH in the endosomes, the ligands dissociate from the receptors. The ligand carried into the lysosomes where it is degraded and the receptor leaves the endosomes and return to the cell surface e.g. LDL, asialoglycoproteins, transcobalamin II, Peptide hormones.

**Route 2: Receptor Recycles, Ligand Recycles**

In this pathway when the receptor-ligand complex reaches the endosomes, they are not dissociated and returns to the cell surface e.g. Transferrin.

**Route 3: Receptor Degraded, Ligand Degraded**

In this pathway, when the ligand receptor complex reaches in endosomes, both the components are degraded in acidic pH possibly as a result of subsequent cotransport to the lysosomes e.g. EGF.

**Route 4: Receptor Transported, Ligand Transported**

In this pathway, the receptor-ligand complex is incorporated into vesicles and carried into the cells e.g. immunoglobulin A (IgA) and immunoglobulin M (IgM).
Folic acid (FA) coupled SLN

Most of the cancer cells in human body including brain have over expressed folate receptors (FR), while they are restricted in normal cells. Folate receptors are the glycosylphosphatidylinositol anchored cell surface receptor. Folate is also known as pteroyglutamate. It is non-immunogenic water-soluble vitamin B that is critical to DNA synthesis, methylation, and repair (folate is used to synthesize thymine). Folic acid is small (441 Da), stable over a broad range of temperatures and pH values and inexpensive. It has high affinity for folate receptors (Kd 10^-10 M). It also retains its ability to bind to the folate receptor after conjugation with drugs with defined conjugation chemistry. After folate attaches to the receptors located within caveolae, it is internalized through the endocytotic pathway. The over expression of these receptors on the surface of many tumor can be exploited to target therapeutic compounds directly to cancerous tissues. It also improves the brain uptake of SLNs.

FA anchored on the surface of SLNs made the nanoparticles has been taken up by the folate receptor which improve the brain uptake of drug in comparison to unmodified SLNs

5-HT moduline

5-HT moduline is an allosteric tetrapeptide modulator. It modify the function of 5-HT1B receptor on inhibiting the binding of 5-HT and generate an antagonist-like effect on the 5-HT1B receptor. The 5-HT1B receptors are expressed on the brain endothelial cells and they play an essential role in physiological evolution. The interaction between 5-HT moduline and 5-HT1B receptor suggested a therapeutic strategy for delivering drugs via the receptor mediated transcytosis pathway. It is used as a ligand for targeting to brain tumor. The 5-HT-moduline-grafted, etopside (ETP) loaded cationic SLNs has been a promising drug delivery carrier for the chemotherapy of brain tumor. An increase in the concentration of 5-HT-moduline reduces the grafting efficiency of 5-HT-moduline, cell viability, and transendothelial electrical resistance of HBMEC monolayer which enhanced the permeability of propidium iodide and ETP across the BBB

Anti epidermal growth factor coupled SLN

EGFR are one of the first molecules targeted by mAb therapy. EGFR are the member of ErbB oncogene family, which consists of four members, namely, ErbB-1, -2, -3, and -4 (also known as HER-1, -2, -3, -4). ErbB receptors are a trans membrane tyrosine kinase normally expressed in epithelial, mesenchymal and neuronal tissues. EGF and anti-EGFR monoclonal antibody are the commonly used EGFR ligands mediating glioma-targeted therapy. EGF also follows the RME pathway. Both EGF and receptor from the EGF/receptor complex are dissociated and degraded in the endosomes after reaching of the complex in acidic pH. It was presumed that the dissociation does not allow the EGF receptor to return to the surface, but rather it is carried further into lysosomes. If the EGF receptor is delivered to lysosomes by vesicular fusion then the cytoplasmic domain of the receptor would remain outside of the lysosome, facing the cytoplasm. Normal cells express up to 1 x 10^5 EGF receptors per cell. However, tumor cells can express up to 200-fold more receptors per cell. Some of the most common EGFR overexpressed are in Glioblastoma (80%) over-expressed epithelial growth factor receptor (EGFR), which is the hallmark for primary glioblastomas. Anti epithelial growth factor factor grafted SLNs encapsulating carmustine has been been target and inhibit the propagation of glioblastoma cells. The surface anti-EGFR has been enhance the transport of carmustine to U87MG cells and subsequently reduces the administered dose

Transferrin conjugated SLN

Transferrin is the best and well known example of receptor-mediated endocytosis, operating in brain endothelial cells. It is a monomeric serum glycoprotein (80 KDa) that binds up to two Fe3+ atoms and they internalized through receptor mediated endocytosis. Transferrin receptors expressed on the luminal membrane of brain endothelial cells. These receptors are also 2 to 10 time overexpressed in most of the tumor cells as compared to normal cells and therefore they are also used as a potential target to enhance carrier for brain tumor cell interaction. When ferrite was conjugated with Tf (holo–Tf), Tf receptors could bind holo–Tf and form clathrin-coated vesicles which carries holo–Tf through the luminal membrane of brain endothelial cells into the endosomes. Once iron carrying transferrin proteins are inside endosomes, the acidic environment favors dissociation of the sequestered iron from the transferrin–receptor complex while the transferrin– receptor complex remains undissociated. Thus, in the endosomes, iron is dissociated from transferrin while the apo-transferrin remains attached to the receptor. Following the release of iron, the apotransferrin/receptor complex is recycled to the plasma membrane, where it is released from its receptor to scavenge more iron and the cycle repeated again. In addition, Tf associated drug carriers were also concluded to benefit the brain targeted delivery.
Table 1.: The various cytotoxic drugs encapsulated by in plain and functionalized SLNs used in brain cancer therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>SLN functionalization</th>
<th>Studies</th>
<th>Results</th>
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<td>Camptothecin</td>
<td>Plain SLNs</td>
<td>Biodistribution</td>
<td>High concentration of camptothecin was found in brain &quot;</td>
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<td></td>
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<td></td>
<td>Camptothecin loaded SLNs showed a good targeting to the brain after iv administration &quot;</td>
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<td>Surface anti-EGFR can enhance the transport of BCNU to U87MG cells &quot;</td>
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<td>Carmustine (BCNU)</td>
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<td>Doxorubicin (Dox)</td>
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<td>Pharmacokinetict behavior</td>
<td>High drug concentration was found in blood, lung, spleen and brain &quot;</td>
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<td></td>
<td>PEG 2000 coated SLNs</td>
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<tr>
<td></td>
<td>PEG 2000 coated SLNs</td>
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<td>Concentration of stealth agent affects the amount of doxorubicin transported into the brain &quot;</td>
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<td>surface anti-EGFR considerably enhances the delivery efficiency of Dox to U87MG cells &quot;</td>
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<td></td>
<td>Cationic SLNs grafted with anti epithelial growth factor (anti-EGFR)</td>
<td>Inhibition against the growth of human GBM U87MG cells, and expression of EGFR on U87MG cells.</td>
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<td>Phenylalanine-coupled SLNs could deliver high amount of drug into the brain tumor cells &quot;</td>
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<td>SLNs could deliver drug into the brain tumor cells &quot;</td>
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<td>SLNs could deliver high amount of drug into the brain tumor cells &quot;</td>
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<td>Paclitaxel</td>
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</table>
Lactoferrin conjugated SLN

Lactoferrin (Lf), also known as lactotransferrin. It is 80KDa glycoprotein belongs to the transferrin (Tf) family. Lf consists of a single polypeptide chain of about 690 amino acids folded into two globular lobes and each of which contains one iron-binding site. It is localized in human brains to neurons, glial cells and microvasculature. In comparison to transferrin, its iron binding affinity is somewhat higher (KD ~ 10–20M). Lf is secreted by the epithelial cells in the exocrine fluids in an iron free form. High concentration of Lf occurs in human milk (1-7mg/ml). Its concentration in the blood is very low (<1µg/ml). Lf receptors (LfR) are present on the BBB. These receptors transport the Lf across the BBB via RMT. LfR are also overexpressed on the cell surface of glioblastomas. The LfR-mediated transcytosis across the BBB has also been demonstrated in vitro and in vivo. Lf has been found as a better ligand for drug delivery into the brain as compared to Tf. Singh et al, was attempted first to use Lf as a ligand for improving the delivery of docetaxel loaded SLN to brain. They prepared the SLN by using stearic acid and modified their surface with Lf. The cytotoxicity studies on the U-87 MG cell revealed the enhanced targeting efficiency of docetaxel on the mentioned cells. The Pharmacokinetic and tissue distribution studies also demonstrated the enhanced docetaxel concentration in brain through Lf conjugated SLNs compared with marketed SLNs formulation.

2. CONCLUSIONS:

SLNs serve as effective and safe carrier for the cytotoxic drug in the treatment of brain cancer. These nanocarriers has been targeted the brain passively as well as actively. Moreover, these carriers are highly flexible and allowing the more tailored approaches for achieving active targeting to distinct brain tumors.

3. REFERENCES

14. Martins SM, Sarmento B, Nunes C, Lúcio M, Reis S, Ferreira DC. Brain targeting effect of camptothecin-loaded solid lipid nanoparticles in rat after intravenous...