INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

LIPOSOMES: RECENT INSIGHT FOR BRAIN TARGETING

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ARTICLE INFO

Article history
Received 02/02/2019
Available online
31/05/2019

Keywords
Liposome,
Brain Targeting,
Peptides,
Oncology,
Neurodegenerative Disease.

ABSTRACT

Present review gives idea about various liposomal systems and their therapeutics in the management of various diseases related with central nervous system. Moreover, the uses of different types of chemicals show their effects at the site of action as well as diagnosis. In addition, therapeutics application of various types of liposomes such as peptide containing, chemical entities and their combination for multifunctional uses have been reported. This review emphasizes the internalization of liposomes inside the different tumor cells. By the application of continuous positive pressure infusion, the technique convection enhanced delivery (CED) has been developed and this technique give the idea about ease of internalization of liposomes through bypassing the blood brain barrier (BBB) in tumor cells.

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*Please cite this article in press as **Dr. Pankaj Nerkar** et al. Liposomes: Recent Insight for Brain Targeting. Indo American Journal of Pharmaceutical Research.2019:9(05).*

INTRODUCTION:

Liposomes are nano-carriers, sphere-shaped, synthetic vesicles, composed of cholesterol (CHO) and amphiphilic phospholipids, and they are the most useful therapeutic and diagnostic (Theranostic) well-known Nano Drug Delivery System (NDDS). These nano-carriers are compatible with bio-molecules, and degraded by bio-molecules, facilitate the trapping of both lipophilic and hydrophilic drugs [1]. Gerald Weissmann proposed the word liposomes composed of two words that is "lipo" means fat and "soma" means body. Conventional liposomes are composed of phospholipid bilayers, and, when administered parentally, are pick up by the reticuloendothelial system (RES) and that leads to shorting of systemic circulation times. Opsonin (a protein found in the serum) recognizes them as outside molecules; due to that liposomes are destructed by phagocytes. For the purpose of increasing systemic circulation time, the surface of liposomes is modified by the polyethylene glycol having the hydrophilic in nature, this leads to increase repulsive force between liposomes and protein (Opsonin) therefore decrease the destruction of liposomes by serum protein. These types of liposomes are called as PEGylated liposomes or stealth liposomes and having the steric hindrance effect this effect avoids the opsonization of liposomes [2].

Most of the time liposomes classified on the basis of inner part that is lamellas and sometime can be classified on the basis of their method of preparation. One is poly-lamellar vesicles (PLVs) included more than 5 lamellas and their size ranges from 100 nm to 1μm and second one is Mono-lamellar vesicles (MLVs) are the mono bilayers structure and again divided into two subcategories as Small mono-lamellar vesicles (SMLVs), size less than 100nm and Large mono-lamellar vesicles (LMLVs), their size ranges from 100-1000nm.

Liposomes may also be classified on the basis of their nature of stimulation like Thermo-sensitive liposomes, Magnetic field sensitive liposomes, Light sensitive liposomes, and Ultrasound sensitive liposomes, these types of liposomes stimulation are carried out by externally.Many types of liposomes can be stimulated by internally, included PH-sensitive liposomes, Enzyme-sensitive liposomes, and Redox-sensitive liposomes [3].

Brain diseases, such as central nervous system (CNS) disorders and brain cancers, are some of the most prevalent, devastating and yet poorly treated diseases. The global drug development for brain diseases has to grow rapidly in the next 20 years as the populations of seniors and patients with CNS disorders are increasing. However, drug development for brain diseases has the poorest success rates compared to other therapeutic areas. The time for developing CNS drugs is normally much longer than for non-CNS drugs. Clinical trials of CNS drugs become challenging because of the complexity of the brain, side effects and the impermeable blood-brain barrier (BBB). In addition to the complexity of brain diseases, the lack of efficient technologies to deliver drugs across the BBB hinders CNS drug development. However, only small molecules that are lipid soluble and also have a molecular weight < 400 Da can cross the BBB; most macromolecules cannot penetrate the brain endothelium. These are the challenges related with the brain so there is ample need to develop such kind of modifications related with the molecules and technique to overcome the problems. The modifications discussed in this review are like ligand attachment, chemical entities, multifunctional liposomes and internalization. These types of modification have been a great impact on the BBB crossing and efficient targeting to the central nervous system. This review discusses recent development in the understanding of the BBB and its disruption in disease conditions. It also focuses on new strategies that have been investigated to deliver therapeutic and diagnostic agents to the brain in the past five years.

Applications of liposomes

Following are some applications of the liposomes:

(a) Intestinal inflammatory disease:

Continual inflammation of the gut mucosa is manifested as either ulcerative colitis or Crohn's disease. A charge reversible liposome incorporated CD40 antisense oligo-nucleotide shown high potency in suppress colitis in animal models and beneficially reduced T lymphocyte activation and after inflammatory cytokine secretion. Level of oxygen radical's important factor in the inflammation of intestinal mucosa and the stress of oxygen reduced by using the tempamine containing liposomes. *Helicobacter pylori* cause the colon related cancer like adenocarcinoma. Clodronate liposomes suppress the colonization of *H.pylori* and avoid the infection related with *H.pylori* [4].

(b) Liposomes in Oncology:

Liposomes drug delivery system having enormous applications in oncology. There are lots of preparation of liposomes for treatment and diagnosis of cancer. In recent era most of liposomes are modified for targeting the cancerous cell. Photosensitizer used for many type of cancer like brain cancer and lung cancer. Temoporfin liposomes and pyropheophorbide is the selective Photosensitizer used in colorectal cancers. Indium-111, Vinorelbine, Rhenium-188 PEGylated liposomes mostly used for both purposes that is radiochemotherapy. Curcumin tested on different cell line of cancer like lung cancer, prostate cancer, cervical carcinoma, osteosarcoma, breast cancer and liver cancer. Low adverse effect, high bioavailability, increase cytotoxicity, enhanced delivery, increase apoptosis, more uptake of cancerous cell [5]. RDP-modified nanoliposomes as curcumin brain-targeting delivery carriers to advance tissue targeting, water solubility, and biocompatibility. Here RDP is used as brain targeting peptide and Rabies virus glycoproteins (RVG) used as ligand to transports nano carriers for treating various brain cancers.

Curcumin-loaded RDP-liposomes (RCL) are significantly inhibits the proliferation of glioma cells and show an observable therapeutic activity against intracranial glioma in the model mice. RDP-PEG-DSPE and NHS-PEG-DSPE these conjugated peptides used for preparation of curcumin liposomes, these agents affect on the stability and targeting of liposomes [6].

(c) Liposomes in neurodegenerative disease:

For the treatment of neurodegenerative disease like Alzheimer's disease(AD), Parkinson's disease (PD), Huntington's disease, nano drug delivery system in the form of liposomes are very significantly developed [7]. Different types of advanced liposomes like stimuli-responsive liposomes including pH, temperature, light, magnetic field, etc types of liposomes are used to treat the symptoms of neurodegenerative diseases. Moreover surface modification or functionalization leads to ease of blood brain barrier crossing. Multifunctional liposomes have enormous effect in the treatment of different symptoms of neurodegenerative disease. For treatment of Parkinson's disease the surface modified liposomes have been developed, chlorotoxin-modified stealth liposomes encapsulating levodopa for the treatment of PD in mice model, and maltodextrin loaded liposomes with co-loading of glutathione as antioxidant have been reported. Modification of liposomes leads to decrease the obstacles comes during their desire action like crossing of BBB, bioavailability, stability, degradation etc [8]. Transferrin functionalized dopamine-loaded liposomes were made by a modified dehydration–rehydration technique, in this type of liposomes many new things have been reported, one is dopamine HCL directly used with transferrin, studied show dopamine can not cross the BBB, due to attachment of transferrin leads to overcome the BBB obstacle, second one is levodopa related complications are also decreases by this type of surface modified liposomes[9]. In the pathogenesis of Parkinson's disease (PD), oxidative stress is one of the important factor that lead to the selective destruction of nigral dopaminergic neurons in PD. Resveriterol studied on different rat model and the outcome show decrease the oxygen radicals and the loss and apoptosis of nigral cells, significantly improved [10]. Several articles have been reported for the treatment of Alzheimer's disease, like transferrin-modified liposome for proficient delivery of a polyphenolic xanthone α-M19. α-M is decreases the cerebral neuronal degeneration, lactoferrin modified procationic liposome, glutathione PEGylated liposome, glucose modified liposome, glutathione PEGylated liposome these types of liposomes also established in several articles [11]. Donepzil liposomes give better bioavailability than the conventional dosage form when it administered intranasally [12]. Multifunctional liposome has also reported for neuroprotective and enhancement in permeation of drug in AD e.g. tacrine HCL [13].

(d) Liposomes for bacterial treatment:

Chloramphenicol (Cm)-loaded liposomes are reported to antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), assess to follicular delivery of Cm loaded liposomes [14]. Emergence of antibiotic-resistant bacteria causes the bacterial meningitis. pH-sensitive liposomes that are fusogenic liposomes have more ability to bind with the bacterial membrane and increase intracellular drug release. Moreover, this capability may be improved by using cell-penetrating peptides (such as Tat47–57, peptide derived from the Tat protein of HIV)[15]. Liposomal gentamicine formulation of particular surface charges like positive, negative, against *Pseudomonas aeruginosa* and *Klebsiella oxytoca* has been investigated [16].

(e) Liposomes for fungal treatment:

Panomycocin is one of the potent antimycotic proteins secreted by the yeast *Wickerhamomyces anomalus* NCYC 434. The development of panomycocin-loaded stratum corneum lipid liposomes (SCLLs) and its determination of antimycotic efficiency against the micro-organism these are Candida *albicans* and *Candida glabrata* clinical vaginal isolates in a human vaginal model[17]. Chitosan containing liposomes with antifungal agent metronidazole are reported, chitosan also capable of antifungal activity and the activity of formulation is determine against *C.albicancs* etc [18]. For treatment of fungal ocular endopthalmitis gold containing liposomes with flucytosine as an antifungal drug has been reported. Here Gold has been used as a tracking agent of drug at the posterior region of eye (rabbit's eye) [19].

Importance of liposomes:

Nano drug delivery system like liposomes have lots of significant effect such as control release of formulation, targeting specific cell like tumor cells, minimum toxicity, more stability, more bioavailability and decrease dose frequency. One more advanced advantages of liposomes, theranostic liposomes that are responsible for both therapeutic and diagnostic purposes. In terms of stability, absorption and distribution in the body, they provide the significant effects, and they carry hydrophilic, hydrophobic and amphiphilic drugs and directly deliver them at the targeted cells [5]. Different types of gases can be loaded into the liposomes like xenon for the treatment of cancer or used for neuroprotective purposes [20]. In order to improve blood circulation and brain-specific delivery, the liposome surface have been modified by the enclosure of macromolecules, such as polymers, polysaccharides, peptides, antibodies, or aptamers [7]. For increase efficient treatment of GI cancer and different types of tumor cells development in the modification of liposomal formulation have been done like surface modification by using different types of polymers, attachment of ligands like peptides antibodies or aptamers or dyes for diagnosis purposes. Microfluidics technique can be also applied for the preparation of liposomes [21].

Need for targeting the brain:

The brain is a more perceptive and frail neuronal organ system that needs a regular supply of fuels, gases, and nutrients to keep up homeostasis and other fundamental functions. But blood brain barrier (BBB) a vascular system of the central nervous system creates a substantial barrier and imposes various obstacles. It decreases the delivery of therapeutic agents to the CNS, including neuroprotective agents, antibiotics, antibodies, to pass through endothelial cell to brain. There are several variables, which affect on the drug delivery or its capability to pass through the blood brain barrier (BBB). So, it is probable that drug may bind to non-transporters in huge amount which cause to be the drug ineffective. Moreover, enzyme action also creates the drug inactive or changes it in a ineffective intermediate molecules. However, membrane barriers inhibit larger size of molecules whereas smaller molecules are passed over to the brain. Likewise, molecules have the charge quickly access into the brain [22]. Hence, lipophilicity does not seem to be required or abandoned factor that may support the drug for safe way to brain [23]. The blood brain barrier (BBB) and the blood brain tumor barrier (BBTB) inhibit therapeutic agent and nano drug delivery systems from entering the brain. For effective transport of therapeutic agent, there is ligand attachment will be needed [24]. Diseases and disorders related with the brain are tremendously complicated to treat pharmacologically because most of therapeutic agents are not capable to enter across the BBB. Composite poly-strand tense junctions between closest cerebral endothelial cells and between choroid plexus epithelial cells make a physical barrier and avoid the way of hydrophilic drug from the blood into the brain, while the inward way of lipophilic drug is limited by drug efflux pumps which act as an efficient barrier [25].

Strategies for targeting brain by liposomes:

Ligands:

An extra level of superiority and specificity for the target cell was achieved with the ligand-mediated targeting, that is defined as active targeting. The purpose is to develop new platforms with increase proper biodistribution, pharmacokinetic properties, and active targeting or desire targeting. Peptides, carbohydrates, glycoproteins, receptor ligands, monoclonal antibodies its parts and growth factors have been useful as ligands. Liposomes used for targeting particular ligands can significantly identify the antigens or the receptors present on the surface of targeted cells or tissues. Because of this more selectivity for cancer cells, approximately all of the administered liposomal drug would gather at the tumor site or targeted site without any harm. Because of this strategy the dose frequency decreases when compared to nontargeted therapies, this leads to a more therapeutic index, with efficient drug efficacy and low side effects.

Ligand-targeted liposomes have established enhanced efficacy over passively targeted equivalents through effective targeting and intracellular accumulation, but they provide idea about new challenges, such as hindered diffusion and penetration through the desire cells, immune recognition, and deactivate through targeting the selective binding of serum proteins. Due to this, ligand-targeted liposome systems have not demonstrated every time successful results in preclinical approaches, and more studies are required to address issues related to their efficiency or targeting characteristic[26].

Peptides:

Blood brain barrier (BBB) inhibits the entry of so many therapeutic agents into the brain. But in recent times, a number of neuroactive proteins of potential therapeutic value have highlighted the important need for efficient and safe transcapillary delivery methods to the brain. Though, most hopeful drug delivery is possible by amplification of pinocytotic vesicles throughout brain capillaries. This is a mechanism of cells which assists in delivering molecules having the large size of neuroprotective potential in conjugated form like peptidomimetic ligands. Afterward these agents bind to specialized peptide receptors, which internalize and transport therapeutic agent in small spherical vesicles across the cytoplasmic brain capillary barrier. These types of conjugates are well-known to be functionally active and efficient in animal models of neurological disease. There are so many research has been investigated for ease of BBB crossing by attachment of ligand in the form of peptide. Glioma is the most hostile and fatal brain tumor in humans, it comprises about 30 per cent of all brain tumors[23].

Table 1: Various peptides reported for brain targeting:

Sr No	Drug	Peptide	Disease	Experimental Model	Targeted site	Effect of modified liposomes	Refrence
1	Epirubicine and Celecoxib	PTDHIV-1 peptide	Brain cancer	glioma-bearing nude mice	Glioma cell	Brain glioma cells and killed glioma cells by direct cytotoxic injury and the induction of apoptosis.	[27]
2	Paclitaxel	cRGD-PEG2000-DSPE and KLA-PEG2000-DSPE	Brain cancer	4T1 tumor xenograft BALB/c mice	Tumor cell	Antiangiogenesis effects without systemic toxicity	[28]
3	Eptifibatide	H102	Alzheimer's disease	AD model rats	Calu-3 cell monolayers	No toxicity on nasal mucosa, H102 could be effectively delivered to the brain and H102 could be effectively delivered to the brain.	[29]
4	Gifitinib	RF (SUV-RF; one _-helical cell-penetrating peptide)	Brain metastasis	BBB Model	bEnd.3 cells	Increase concentration across BBB and efficient action	[30]
5	Fluorophores	(CDX) and c(RGDyK) (RGD)	Brain cancer	Using human umbilical vein endothelial cells as BBTB model	Glioma cell	Liposomes and disks are present in the cytoplasm as their intact forms and traverse the BBB	[24]
6	Levodopa	chlorotoxin	Parkinson's disease	methyl-phenyl-tetrahydropyridine (MPTP)-induced PD mice	brain microvascular endothelial cells	ClTx-modified LS might serve as a targeting delivery system to transport more drugs into the brain for a better PD therapy.	[8]

Chemicals:

Different types of chemical entities which are used for modification of liposomes for targeting delivery system. These modifications affect on the stability, compatibility, efficacy, of liposomes. Chemical entities included maltodextrin, poly ethylene glycol, transferrin, hyaluronan, glutathione, surfactant etc. These agents also affect on the permeation of drug molecules into the blood brain barrier (BBB) and give the targeted desire effect. Modification with the help of chemical entities leads to binding at the specific site of brain tissue and that cause the permeation, efficient action of targeted molecules. Liposomes are biocompatible, biodegradable, non-immunogenic, and non-toxic drug transport systems. Liposomes are targeted to brain using receptor-mediated endocytosis advanced by combine with particular molecules like monoclonal antibody (OX26)8, and glucose. One of these molecules is maltodextrin, which is also be readily used as a basic component of several targeting system.

Table 2: Chemical origin materials which are used for liposomes targeted delivery.

Sr no	Drug	Chemical entities	Disease	Experimental Model	Targeted site	Effect of modified liposomes	Reference
1	Dopamine HCL	Transferrin	Parkinson's disease	BBB	Cerebral microvascular endothelial cells (hCMEC/D3)	Improving benefits and decreasing complications to patients subjected to L-dopa chronical treatment.	[9]
2	Curcumin	*p*-aminophenyl-α-d-mannopyranoside	Brain cancer	Brain glioma bearing mice	Brain glioma cell	Increase the survival period of brain glioma-bearing mice and inhibit the growth of gliomas	[31]
3	Donepzil	PEG	Alzheimer disease	Male Wistar rats	CNS	High encapsulation efficiency (84.91%±3.31%) and sustained-release behavior, safe and free from toxicity	[12]
4	Galanthamine Hydrobromide	Propylene glycol and dehydrated alcohol	Alzheimer disease	Rat brain	BBB	Efficiency of acetylcholinesterase inhibition of GH was greatly enhanced by intranasal administration and less toxic	[32]
5	Neurone growth factor	Lactoferrin	Alzheimer disease	human brain-microvascular endothelial cells (HBMECs and Ab1-42-insulted SK-N-MC cells	BBB	to target the BBB and inhibit the Ab-induced neurotoxicity	[33]
6	Ginkolide	Borneol	Ischemic stroke and Cerebral infarction	Mice	BBB	Borneol significantly promoted the transport of ginkgolide across the BBB	[34]

Multifunctional liposomes:

Multifunctional liposomes able detect and specially deliver therapeutic agent at site of diseased cell with the help of ligand and biomarkers. Multiple feature containing liposomes can be obtain by using one for therapeutic purposes and second one for the diagnostic purposes just like in case of theranostic liposomes. For modification of liposomes into the multifunctional liposomes there are many types of peptides are required , several approaches have been done by using two types of peptides one leads to ease in BBB crossing and one target the particular site may be receptors or other binding site present on the cell or tissue. Peptides are also giving the effect of inhibition of particular secretion and permit the functionalized liposomes across the BBB. These types of approaches very efficient in the case of targeting brain cancer or target the internal structure of liposomes. Multifunctional liposomes destroy brain aggregates and increase peptide elimination across the BBB and its peripheral clearance. This all-in-one multifunction therapeutic device can be considered as a candidate for the treatment of Alzheimer's disease [35].

Table3: Multifunctional liposomes.

Sr no	Drug	Peptides or Chemical entities	Disease	Experimental model	Targeted site	Effect of Modified liposomes	Reference
1	Vinblastine	TfR-T12 and octa-arginine conjugate stearyl-R8	Brain cancer	Brain glioma-bearing mice	Glioma cell	Across the BBB, killing brain glioma and glioma stem cells via the induction of necrosis, apoptosis and autophagy	[36]
2	Doxorubicin	Cyclic RGD (c(RGDyK)) and p-hydroxybenzoic acid (pHA)	Glioblastoma	Nude mice bearing intracranial glioma	Glioma cell	Increase the cytotoxicity of doxorubicin and penetrate the glioma cell	[37]
3	Doxorubicin	Transferrin–cell penetrating peptide–sterically stabilized liposome (TF-CSSL),	Brain cancer	BALB/c nude mice	Brain microvascular endothelial cell and C6 cell	Crossing the BBB and entering into glioma C6 cells	[38]
4	Epirubicin	Aminophenyl glucose and cyclic pentapeptide	Brain cancer	glioblastoma-bearing mice	Glioblastoma cell	Less leakage, cross BBB,destroying glioblastoma cell	[39]
5	Vinorelbine and tetraandrine	(CHOL- PEG2000- PEI) and (TPGS1000- VAP)	Malignant bran glioma	Glioma bearing mice	Brain glioma	Liposomes accumulates into brain tumor location, show specificity at tumor site and efficacy	[40]
6	Ursolic acid	Epigallocatechin-3-gallate (EGCG	Brain glioma	Glioma bearing mice	C6 glioma cell	Cross BBB, increase therapeutic effect on C6 glioma cells	[41]
7	Daunorubicin and quinacrine	Wheat germ agglutinin and tamoxifen	Brain glioma	Intracranial glioma-bearing ICR mice	Glioma cell and glioma stem cell (GSC)	Cross BBB,killing glioma cell and GSC cells	[42]

Internalization:

In this phenomenon, liposomes are grafted with several types of targeting ligands or molecules, such as peptides, aptamers, antibodies and its parts, etc., using several surface engineering techniques. When modification of liposomes deals with surface these types of approaches has played an important role in preparation of a liposomal drug delivery system for significant targeting, endocytosis and therapeutic effects. Modification of liposomes in terms of surface by using variety of techniques have aided in addressing the recent confines of liposomes.

Liposomes may be engineered for more application by using modified surface functionalization and modification techniques, elaborating the significant benefits in oncology for long time circulation, more cellular-intake, higher freight gathering at tumor site, without lysosomal degradation and stimuli responsive effects. The recent modified technique that is intracellular targeting or internalization over articulated receptors present in cytoplasm and nucleus; cell organelle targeting; and tumor-microenvironment or vasculature targeting become a more significant platform for modification of liposomes. Cell-penetrating peptides (CPPs) having capability of cell penetration, internalization, and endosomal escape have significant prospect in drug delivery systems.

Internalization of liposomes by Convection Enhanced delivery (CED):

The BBB create the obstacle for chemotherapeutic drug that cause to reduce the efficiency of drug and limit accumulation of drug in tumor of targeted cell. To avoid these obstacles the current approach that is "Convection enhanced technique" (CED) have great platform for functionalization and modification of liposomes. There are several drug have been investigated by using this technique like Cisplatin and Carboplatin for different types of glioma bearing mice model. Several affects have been seen by using this technique like survival time of rats increases and efficacy also [43, 44]. Convection-enhanced delivery (CED) bypasses the BBB by delivering agents directly into the tumor and nearby parenchyma. By the application of continuous positive pressure infusion in convection enhanced technique leads to increase distribution of formulation at the targeted site. While optimistic delivery of drug method in concept, the administration of drugs via CED is very efficient for brain targeting. Recently, CED has been applied on human subjects those are suffering from neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease and nuero-oncology. CED used for clinical trials of several agents like conventional chemotherapies, cytotoxin-ligand conjugates targeting cell surface receptors, monoclonal antibodies with or without radioactive isotope conjugates, antisense oligonucleotides, and liposomal vectors engineered to deliver gene therapy have been conducted [45]. CED can be maximize the drug delivery to cancerous cells, reaching more therapeutic concentration and decreasing or avoid systemic side effects.

For choosing an anti-cancer agent for CED in the brainstem, one should consider the robust structures of the brainstem. Convection-enhanced delivery (CED) is a precise technique that creates a pressure difference at the tip of an infusion catheter to deliver therapeutics agents directly through the interstitial spaces of the central nervous system [46].

Table 4: Drugs used for internalization of liposomes.

Sr no	Drug	Peptides or Chemical entities	Disease	Experimental model	Targeting site	Effect of liposomes after Internalization	Reference
1	Curcumin	Brain-targeting peptide RDP	Glioma	Glioma bearing mice model	Glioma cell	Prolonged the survival time of the glioma-bearing mice from 23 to 33 days, and the inhibition mechanism of the RCL on glioma cell	[6]
2	Epirubicine and Celecoxib	PTDHIV-1 peptide	Brain cancer	Glioma bearing mice	Glioma cell	Internalized by brain glioma cells and killed glioma cells by direct cytotoxic injury and the induction of apoptosis.	[27]
3	Doxorubicine	TF-CPP-SSL),	Brain cancer	Brain microvascular endothelial cell and C6 cell	Glioma cell	Transported across the BBB without drug leakage, liposome breakup, or cleavage of ligand	[38]

ACKNOWLEDGEMENT

Authors are grateful to Principal and Management of R. C. Patel Institute of Pharmaceutical Education & Research for providing all the necessary facilities for carrying out this study.

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