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The role of lipid based nanoparticles in brain targeted drug delivery system: An overview

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***Abstract*---**Recently, targeted drug delivery systems have gained muchimportance fordeliveringmany kinds of drugs as well as imagingagents,particularly to the targetedDisease cells or tissues. The diagnosis and treatment of brain disorders is an extremely challenging task. The blood-brain barrier (BBB) is the primary obstacle in conveying the chemotherapeutic and diagnostic agents that prompt the insufficient delivery of drug at the brain-targeted site. Many drug molecules are non-soluble in aqueous systems, unable to cross BBB, or present severe side effects. Lipid-based nanoparticle (LBNP) systems represent one of the most potential colloidal carriers. They are preferred over polymeric nanoparticles due to their high stability, excellent targeting ability,increased loading capacity, non-toxicity, low production costs, and ease of preparation. Combining drug with lipid

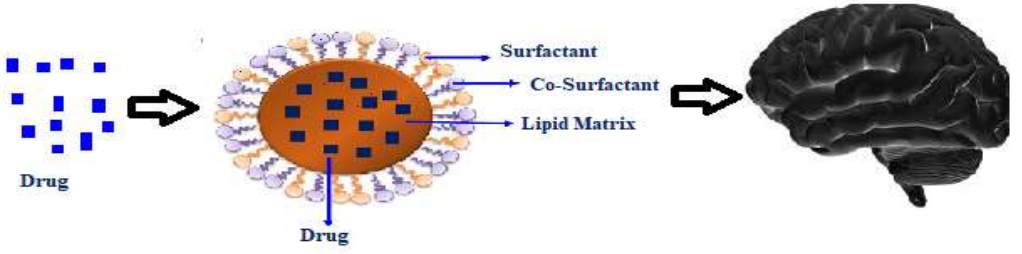
nanoparticles reduces the therapeutic dose and toxicity, decreases drug resistance, and increases drug levels in the targeted tissue. This review presents the different types of LBNPs developed in recent years and theirapplication in brain disorders.

***Keywords*---**blood-brain barrier, chemotherapeutic, lipid-based nanoparticles, tumour, Parkinson's disease.

Introduction

Nanotechnology has evolved rapidly in the past two decades and has been used mainly to diagnose and treat diseases. Nanoparticles(NPs) are about 1 and 1000 nm in size and enhance the bioavailability of drug drugs and the selectivity of drugs (García-Pinel et al., 2019). NPs provide many benefits, including improving solubility, protecting the load from enzyme destruction, and enhancing targeting efficiency. NPs in the area of medicine and research have also increased consideration (Gao, 2016).

Multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease, stroke, and brain tumors are currently disordered by the Central Nervous System (CNS), with much consideration and focus. Chemotherapeutic agents, specifically for the brain, must be administered for successful diagnosis and treatment of brain tumors. However, only small lipophilic molecules (<500 da) can effectively cross the BBB and enter an appropriate brain concentration other than nutrients. Due to drug transportation restriction into the brain by blood-brain barriers (BBBs), different techniques have been developed using NPs as carriers (Pardridge, 2007). Several nanoformulations used here are lipid formulations since the preparation and replacement compositions have made incredible advances in recent years.



Brain Drug Delivery Obstacles

Barrier to the Blood-Brain

BBB is the most crucial obstacle in the delivery of brain-driven drugs. In 1885, Ehrlich discovered that intravenously infused dye could label most of the organ, except the brain. BBB consists of different cells, including brain endothelial cells, pericytes, astrocytes and neuronal cells. BBB consists of different cells. Consistent tight intersections between BCECs prevent paracellular transport from blood to mind. Moreover, these close intersections create very high

transendothelial electrical resistance (TEER) between blood and the brain and considerably reduce the passive dissemination of compounds. Despite the restriction, various carriers may interfere in entering or expelling multiple substances from the brain (Gao, 2016; Teleanu et al., 2018).

Barrier to Blood Brain Tumor

In brain tumors, the core of the BBB is undermined but is essential in the environment. The delivery of drugs to brain tumors is smaller than peripheral tumors. BBTB has a small pore size and a higher level of drug efflux pumps, including P-glycoprotein, multidrug resistance-related proteins, and the breast cancer resistance protein relative to the blood tumor barriers in peripheral tumors (Wolburg et al.,)

Brain Barrier Nose

The nasal cavity's structure, physiology and brain delivery path have all been measured. The respiratory and olfactory regions are responsible for the brain or blood absorption of the medicine. Some compounds may reach the systemic circulatory system via the respiratory mucosa and cross the BBB into the brain. Some can be directly transported to the brain through trigeminal nervous pathway or lamina propria adsorption from perivascular and lymphatic spaces. The olfactory mucosa pathway mediates medicine from the nasal cavity to the brain very rapidly (Gao, 2016).

Barrier to Blood-Cerebrospinal Fluid(BCSFB)

The BCSFB is an obstacle to the introduction of drugs into the CNS. It consists of the plexus epithelial cells that prevent molecules from entering. Due to the inconsistency between interstitial fluid and CSF, the CSF-brain barrier has been established. The presence of polarised endothelial cells connected by near junctions in BBB results in low permeability. It restricts medication delivery to the central nervous system (CNS) (Hangargekar et al., 2019).

Approaches to overcome the BBB

The BBB is the first barrier in the brain delivery of medicines. Researchers have developed different techniques to circumvent or bypass BBB, including cellular internalisation, opening, and intranasal delivery by BBB (Gao, 2016). Various brain transporters are listed in Table 1

Table 1: Transporters of Blood Brain Barrier

Receptor Mediated Transport	Active Efflux Mediated Transport	Transporter Mediated Transport
Transferin receptor	Adenosine triphosphate-binding cassette (ABC) transporter	Glucose transporter, member 1
Insulin Receptor	P-glycoprotein	Large neutral amino acid Transporter, member 1
Low-density lipoprotein	ABC transporter	

receptor-related protein	subfamily G, member 2	
Nicotinic acetylcholine receptor	Organic anion transporter	Cationic amino acid transporter, member 1
Insulin-like growth factor receptor	Organic anion transporting polypeptide	Monocarboxylic acid transporter, member 1
Diphtheria toxin receptor	Glutamic acid, amino acid transporter	Concentrative nucleoside transporter
Scavenger receptor call B type	Taurine transporter	Choline transporter
Leptin receptor		Nucleobase transporter
Neonatal Fc receptor		

Lipid-BasedNanoparticles

Lipid-based nanoparticles (LBNPs) is highly regarded in drug discovery and cancer treatment. These nanoparticles can transport hydrophobic and hydrophilic molecules, show very low to no toxicity, and increase drug action time through extended half-life and controlled drug release (García-Pinel et al., 2019).

Liposomes

Liposomes are the drug delivery system most studied due to their biocompatibility and biodegradability (García-Pinel et. al., 2019). These are synthetic and spherical cells composed of single amphiphilic lipid bilayers that may carry drugs, vaccines, nucleic acids, aptamers, antibodies and protein molecules (Teleanu et al., 2018). They develop vesicles in water, enhance drug solubility and stability, and encapsulate hydrophobic or hydrophilic drugs. Cholesterol-modified liposomes consist of a multiple bilayer with sizes between 0.5 nm and 10 nm, called Multilaminar Vesicles (MLVs); a single bilayer with sizes above 100 nm, called Large Unilamellar Vesicles (LUVs); and intermediate sizes (10–100 nm) called Small Unilamellar Vesicles (SUVs) (Yingchoncharoen et. al., 2016).

Nanocarrier vectorisation has two methods. One is passive targeting that occurs by molecular movement through the cell membrane, and the other is active targeting, where liposomes loaded with antibodies recognising disease cells. Temperature, pH or magnetic fields are parameters that can be altered by an external stimulus for controlled drug delivery (García-Pinel et al., 2019).

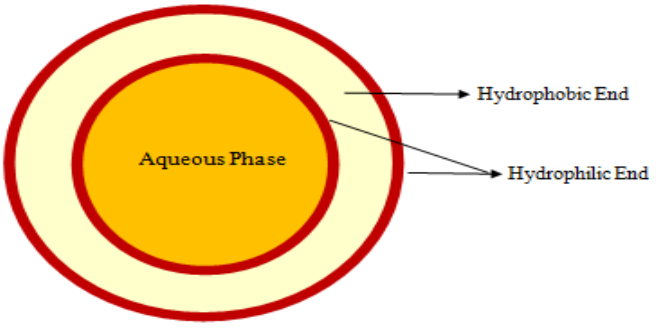


Figure 1: Liposome

Liposomes are mostly used in target brain therapy, due to the abilityof crossing the blood-brain barrier. Many studies have reported the use of liposomal formulations to deliver drugs, such as mitoxantrone, 5-fluorouracil, paclitaxel, doxorubicin, erlotinib, opioid peptide and monoclonal antibodies as summarised in table 2.

Table 2: Liposomes Based Formulations for Brain Targeted Drug delivery System

Sl. No.	Lipid	Preparation Method	Drugs	Comments	Reference
1	PFV-PEG(2000)-DSPE	Nucleophilic substitution reaction	Doxorubicin and Erlotinib	Higher translocation of dual functionalised liposomes across the BBB and delivering chemotherapeutic drugs to the glioblastoma tumor cells	Lakkadwala et al., 2019
2	PEG(2000)-DSPE	Thin-film hydration method	Temozolomide	Reduced tumour growth and significantly prolonged survival of glioma-bearing mice	Papachristodoulou et. al., 2019
3	DOPE DOTAP,	Thin lipid film hydration method	Penetratin	Multifunctional liposomes provide an excellent gene delivery platform for neurodegenerative diseases	Rodrigues et al., 2018
4	PEG-DSPE	Ethanol injection method	HAIYPRH	Potential targeted drug delivery system of ischemic stroke treatment	Wang et al., 2015
5	DMPC and EYPC	PEG	Antibody	Specific delivery of single domain antibody fragments over the BBB	Rotman et al., 2015
6	SPC, DSPE	Repeated freeze-thawing method	^{188}Re	Significantly prolong the lifespan of rats while maintaining	Huang et al., 2015

				systemic Radiation safety.	
7	DPPC and PEG	Freeze-drying method:	Tacrolimus	Enhanced the therapeutic Efficacy; promising neuroprotectant after cerebral stroke.	Ishii et al., 2013
8	PC-E	Lipid film hydration	Mitoxantrone	Significantly improve the therapy of brain metastasis	Orthmann et al., 2012
9	PEG		Opioid peptide DAMGO	Promising platform for enhancing and prolonging the delivery of drugs to the brain.	Lindqvist et. al., 2012
10	DSPE-PEG2000 and DSPEPEG2000-maleimide		Monoclonal antibody	Sustained therapeutic effects are achieved. Both dose-response and time-responses are observed	Xia et. al., 2008

DAMGO:H-TyrD-Ala-Gly-MePhe-Gly-ol;DOPE: Dioleoylsnglycero3phosphoethanolamine; DOTAP: Dioleoyl-3-trimethylammoniumpropane chloride; DMPC: 1,2-dimyristoylsnglycero-3-phosphocholine;DSPE:1,2-distearoyl-snglycero-3-phosphoethanolamine-N[carboxy(polyethylene glycol)-2000];

DPPC:Dipalmitoylphosphatidylcholine ; EYPC: eggyolk phosphatidylcholine;PC-E**:** Phosphatidylcholine; PEG: Polyethylene Glycol;RGD: Arginine-lysine-aspartate; SPC: Soy phosphotidylcholine; T7-P-LPs: T7-conjugated PEGylated liposomes; Tf: Transferrin.

Solid Lipid Nanoparticle

In 1991, solid lipid nanoparticles (SLNs) were introduced as an alternative to conventional colloidal carriers such as emulsions, liposomes, polymeric-micro and nanoparticles. SLNs are consisting of physiological lipids that can be dissolved or spread in a solid-state at room and body temperature. These particles range from 50–1000 nm (Bagul et al., 2018).

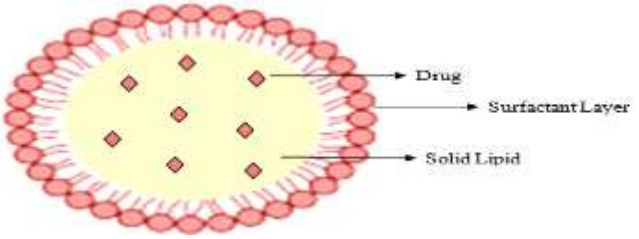


Figure 2: Solid nanoparticles

The vital monolayer phospholipid forms a grid material for drug encapsulation, including mono-, di- or triglycerides, fatty acids and complex glyceride mixtures, balanced by surfactants or polymers that allow them to cross tight BBB endothelial cells and escape the reticuloendothelial system (RES). During manufacture, the soft lipids were combined with the medication and distributed by high-pressure homogenisation or micro-emulsification into an aqueous surfactant (Masserini, 2013; García-Pinel et al., 2019; Hangargekar et al., 2019). SLNs have significant advantages such as site-specific targeting, the possibility of lyophilisation, increased stability, controlled release of lipophilic and hydrophilic drugs, no special requirement for solvents, low cost, fast preparation and non-toxic (García-Pinel et al. 2019; Hangargekar et al. 2019). SLNs have bad effects on human granulocytes. This all makes them an effective candidate for drug delivery systems. In comparison, SLNs have some drawbacks, such as moderate drug-loading ability, drug expulsion due to crystallisation under storage conditions, and particle growth (García-Pinel et al., 2019). Table 3 offers a few examples of SLN-based formulations for brain-targeted drug delivery.

Table 3: SLN Based Formulations for Brain Targeted Drug Delivery System

Sl. No.	Lipid	Preparation Method	Drugs	Comments	Reference
1	Stearic acid, borneol, puerarin	Emulsification evaporation-low temperature solidification method	*Pueraria* flavone	More pronounced accumulation and a promising therapeutic carrier for brain disease	Wang et. al., 2019
2	Tween 80	Solvent Injection Method	Nifedipine	Enhanced site-specific delivery to the brain	Bhargava et al., 2018
3	Gelucire 43/01 Geleol and Precirol	Emulsification solvent evaporation technique	Agomelatine	Effectively enhanced both the absolute bioavailability and the brain delivery	Ahmed et al., 2017
4	TPM, DSPE	Homogenisation followed by	Carmustine	Higher BBB permeability.	Kuo et al. 2016

		centrifugation		Superior anti-proliferative action	
5	Cetyl Palmitate	High shear homogenisation followed by sonication technique	Resveratrol	A promising strategy for resveratrol delivery into the brain, and protection from degradation	Neves et. al., 2016
	POPC, DSPE, CHO, DM	Detergent dialysis technique	siRNA	Higher uptake and gene knockdown efficacy with an increase in the uptake of the LNPs.	Brunn et al., 2015
8	Stearic acid, DDAB, Compritol 888	Solvent displacement technique	Vincristine and temozolomide	Outstanding drug delivery system to achieve excellent therapeutic efficiency	Wu et al., 2015
9	Compritol 888, Precitol	Modified emulsification–diffusion technique	Haloperidol	Effective drug the delivery system for psychiatric conditions	Yasira et al., 2014
10	CP, DMPC	High shear homogenisationand ultrasonic techniques	Camptothecine	Enhanced accumulation of camptothecine, Superior *in vitro*antitumour activity	Martin et al., 2013
11	Glycerol tristearate	Thin-layer ultrasonication technique	5-fluoro-20-deoxyuridine	Increased penetration through the blood-brain barrier	Wang et al., 2002

CHO: Cholesterol; DO-FUdR: 3,5-dioctanoyl-5-fluoro-2-deoxyuridine; DM: Dimyristoyl; DSPE: 1,2-distearoyl-snglycero-3- phosphoethanolamine-N-[carboxy(polyethylene glycol)-2000]; DDAB: dimethyldioctadecylammonium bromide; DMPC: 1,2-dimyristoyl-sn-glycero-3-phospho-choline;Lf:Lactoferin;POPC: 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; Tf: Transferin; TPM: Tripalmitin

Nanostructured carrier

Nanostructured lipid carriers (NLCs) are the recently formed colloidal lipid carriers that spread partly crystallised lipid nanoparticles in an aqueous dispersion medium. NLCs have higher drug load potential and resist lipid crystallisation due to the inclusion of liquid lipids in NLC formulation. NLCs are a mixture of lipids such as glyceryl tricaprylate, ethyl oleate, isopropyl myristate and glyceryl oleate. The mean particle sizes range from 10–1000 nm and are influenced by the design of the lipids and manufacturing process.

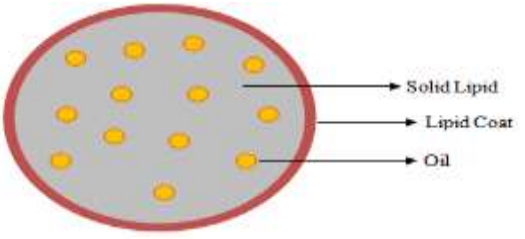


Figure 3: Nanostuctured Lipid Carrier

The key advantages of these nanoparticles are: they can be loaded with hydrophilic and hydrophobic drugs, surface-modified, site-specific targeting, drug-release regulation, and low in vivo toxicity. However, the drawbacks of these nanoparticles are low loading potential and drug expulsion after polymorphic lipid transfer from the nanocarrier matrix during storage (García-Pinel et al., 2019).

Because of its lipid nature, it can triumph over BBB's barrier role in brain tumour therapy. The surface-modified NLCs display superior tumour targeting ability. Studies showed NLCs could be used to enhance drug bioavailability. Among the contributions recorded in recent years is paclitaxel, which, together with triolei in an NLC, may be used as a candidate for cancer therapy due to possible drug delivery to the brain (Emami et al., 2017). Table 4 summarises various NLC-based formulations.

Table 4: NLC Based Formulations for Brain Targeted Drug Delivery System

Sl. No.	Lipid	Preparation Method	Drugs	Comments	Reference
1	Span 80, PEG 400	Hot, high-pressure homogenisation technique	Indinavir	Displayed significantly higher and augmented concentrations in the brain	Nasiri et al., 2019
2	Span 80, PEG 400	Hot homogenisation, rapid ultra-sonication	Quetiapine Fumarate	Potential drug delivery system through intranasal route	Sivadasu et al., 2019
3	CHO, triolein,	Solvent evaporation	Paclitaxel	The potential delivery system	Emami et al., 2017

	stearylamine	method		in brain cancer cells	
4	DMSO	Solvent diffusion method	Temozolomide	Efficient in selective delivery into U87MG cells	Song et al., 2015
5	Tripalmitin, oleic acid, polysorbate 80	Hot high-pressure homogenisation technique	Curcumin	The plasmid concentration was highly increased via intraperitoneally after loaded with NLC.	Chen et al., 2015

CHO: Cholesterol; DMSO: Dimethyl Sulfoxide; PEG: Polyethylene Glycol; RGD: Arginine-glycine-aspartic acid peptide; Tf: Transferin.

SLNs and polymeric nanoparticles are favoured to supply anticancer drugs (Qu et al. in 2016 and Wu et. al. in 2015). In a gliomatosis cerebri treatment trial, three separate nanocarriers (SLN, NLC, and polymeric nanoparticles) were developed to deliver temozolomide (TMZ). Unlike TMZ-SLN and TMZ-polymeric nanoparticles, the formed TMZ-NLCs showed prevalent apoptotic activity against glioblastoma multiforme (GBM) cells. TMZ-unrivaled NLC's in vitro apoptotic activity was attributed to its simpler entry and higher drug load (Song et. al., 2015).

Due to curcumin's low bioavailability and hasty in vivo metabolism, its chemotherapeutic application became risky. Thus, curcumin-exemplified NLCs were formed with a 6.4-fold increase in plasma concentration. Because of increased bioavailability and tumour efficacy targeting, the brain and tumour performance was dramatically upgraded. Curcumin-stacked NLCs can be used in brain tumour targeting (Chen et. al., 2016).

Niosomes

Niosomes are microscopic lamellar vesicles formed by alkyl or dialkyl polyglycerol ether (non-ionic surfactant) and cholesterol. These are structurally similar to liposomes, but the key difference is that they contain non-ionic surfactant rather than phospholipid. They offer various advantages such as compatibility, non-immunogenicity, the ability to integrate hydrophilic, lipophilic and amphiphilic drugs, brain-specific drug choices, reduced dose and dosage frequency, higher stability, better bioavailability and delayed clearance (Das & Palei, 2011). Thus, liposomes are better favoured (El Maghraby et. al., 2009).

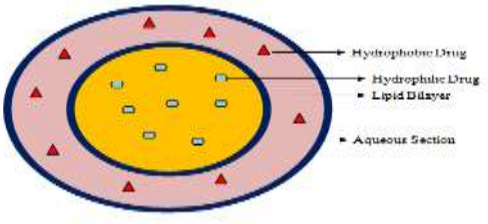


Figure 4: Niosome

Ferrociphenol (Fc-diOH), an organometallic complex has potent antitumor activity. Fc-diOH stacked LNCs encapsulated inside the marrow-isolated adult multilineage inducible (MIAMI) cells were developed for targeted delivery of Fc-diOH to the brain tumour cells. MIAMI cells can relocate to the synapses crossing through the BBB. Thus, utilising MIAMI cells as a carrier for lipid nanocapsule could support brain targeted delivery of the chemotherapeutic agent in the treatment of brain tumour. Cytotoxicity study revealed that internalisation of FcdiOH-LNCs did not improve MIAMI cell death (Roger et al., 2012).

In another study, cannabidiol-decorated and an antidepressant loaded LNCs were developed and evaluated in an animal model. The LNCs were administered through i.v.Injection. Healthy mice receiving coated LNCs were not observed to have any toxicity. This study widens with cannabinoids the yet scarce

Table 5: Niosome, LNC and LPHN Based Formulations for Brain Targeted Drug Delivery System

Sl. No.	Lipid	Preparation Method	Drugs	Comments	Reference
1	Span 60 and cholesterol	Ethanol injection method	Bromocriptine Mesylate	Enhancement in brain distribution and improved pharmacodynamic behavior with 10 times dose reduction	Sita et. al., 2020
2	Sorbitan esters and cholesterol	Film hydration method	Rivastigmine	A good candidate for new drug delivery system.	Estabragh et. al., 2018
3	Cholesterol	Thin-film hydration method.	Temozolomide	Enhanced permeation into brain because of surface modification	De et. al., 2018
4	Span 20, 60, 80, tween 20, 80 and cholesterol	Lipid layer hydration technique	Folic acid	The release of drug followed anomalous diffusion and obeyed first order release kinetics.	Ravouru et. al., 2013

Lipid Nanocapsules

These are the submicron particles comprised of lipid and mixed with polymer, vitamins, proteins, amino acids etc. Lipid nanocapsules (LNCs)are promising DDS for conventional small anticancer drugmolecules.

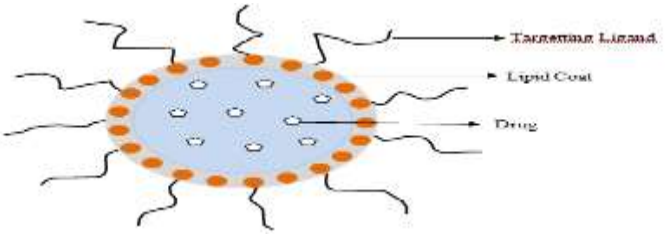


Figure 5: Lipid Nanocapsule

Ferrociphenol (Fc-diOH), an organometalliccomplex has potent antitumor activity. Fc-diOHstackedLNCs encapsulated inside the marrow-isolated adult multilineage inducible (MIAMI) cells were developed for targeteddelivery of Fc-diOH to the brain tumor cells. MIAMIcells can relocate to the synapses crossing through the BBB. Thus, utilising MIAMI cells as a carrier for lipidnanocapsule could support brain targeted delivery of the chemotherapeutic agent in the treatment of brain tumor. Cytotoxicity study revealed that internalisation of FcdiOH-LNCs did not improve MIAMI cell death (Roger et. al., 2012).

In another study, cannabidiol-decorated and an antidepressant loaded LNCs were developed and evaluated in animalmodel. The LNCs were administered through i.v. injection. Healthy mice receiving coated LNCs were not observedto have any toxicity. This study widens with cannabinoids the yet scarce armamentarium of exogenous and nonimmunogenic ligands available for brain targeting. Finally, the consistency of the results served to validate a versatile screeningmethod to evaluate the passage of nanocarriers across the BBB (Aparicio-Blanco et. al., 2019).

Lipid Polymer Hybrid Nanocarrier

These are hybrid lipid-polymeric system made up bymixing lipids and polymers and served as an efficient carrier for delivering drugs as well as genes. These were introduced to avoid drawbacks associated with colloidal lipidnanocarriers and other polymeric nanoparticles. LPNsconsist of two major parts: polymer and the lipid component.A typical LPN has a center shell structure. Thepolymeric core is used for loading various small moleculedrugs and diagnostic agents and the lipid shell is used to confer stability and suitable biocompatibility (Wakaskar et. al., 2018).

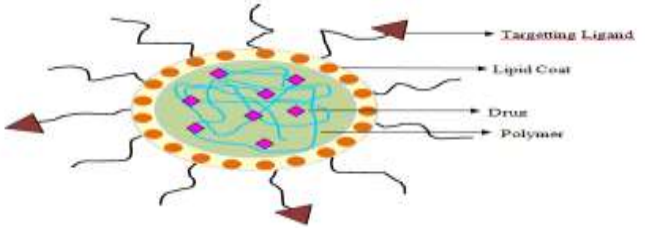


Figure 6: Lipid Polymer Hybrid Nanocarrier

Combination therapy of chemotherapeutic agent and nucleic acid significantly solved multidrug resistance issues in cancer. Pemetrexed (PTD) and miR-21

antisense oligonucleotide (anti-miR-21) co-encapsulated in lipid-polymer hybridnanoparticles (LPHN) were developed for targeted deliveryto the brain for the treatment of glioblastoma. The LPHN showed superior antitumoractivity by increasing the cellular uptake from 6% to 78%. Higher bioaccumulation of PTD and anti-miR-21 in U87MG cells were achieved upon administration of LPNs, which was essential for the treatment of glioblastoma (Küçüktürkmen et. al., 2017).

Conclusion

The combination ofthe principle of nanotechnology and colloidal lipid carrier systems has modernised the pattern of chemotherapeutic approachesin the treatment of numerous pathologies, especially inbrain tumour cases. Though the current therapeutic approach using polymeric nanoparticle carriers for brain tumour cases is efficient, it is related to severe and disturbing side effects. In customised medicine, lipid-based nanocarriers have shown promising clinical outcomesas they can distinguish and screen mind tumour treatment adequately in an early stage.

Lipid-based nanoparticles open new channels for drug delivery to the brain like antitumour, antianxiety,antibiotics, antipsychotics etc. Liposomes are the most broadly utilised LBNPs because of their extraordinary biocompatibility. Recent achievements in operating SLNs and NLCs have also been increasing exceptional consideration. Niosomal carriers for intranasal administration are also promising approaches for delivering neurotherapeutic agents via direct nose to brain route.

More work is still neededto better understand the absorption enhancing mechanisms of lipids to fulfil regulatory guidelines for characterisation and stability enhancement of lipid-based formulations.This review suggested that lipid-based nanoparticles could be a more promising candidate than others for effective management of diagnosis and therapy of brain disorders.

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