

How to Cite:

Kumar, K. P., Nihal, P. ., Bandari, N., Iswariya, V. T., Rao, A. H. om P., Rana, R., & Kaushik, S. (2022). The role of lipid based nanoparticles in brain targeted drug delivery system: An overview. *International Journal of Health Sciences*, 6(S4), 2924–2940. <https://doi.org/10.53730/ijhs.v6nS4.8628>

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

K. Praveen Kumar

Govt of NCT Delhi, DPSRU, NewDelhi

Nihal. P

National College of Pharmacy, Kozhikode, Kerala

Neeraj Bandari

Arni School Of Pharmacy, Kangra Himachal Pradesh

V. T Iswariya

CMR College of pharmacy, Hyderabad, Telangana

A. Hari om Prakash Rao

Research Scholar, Gandhi Nagar, Rushikonda, Visakhapatnam, Andhra Pradesh 530045

Ritesh Rana

Himachal Institute of Pharmaceutical Education and Research (HIPER), Bela Nadaun

Sumit Kaushik

Faculty of Pharmacy ,Raja Balwant Singh Engineering Technical Campus, Bichpuri, Agra

Abstract---Recently, targeted drug delivery systems have gained much importance for delivering many kinds of drugs as well as imaging agents, particularly to the targeted Disease 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

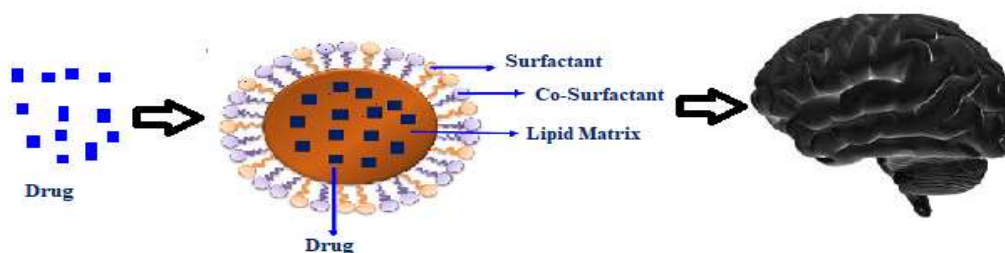
nanoparticles reduces the therapeutic dose and toxicity, decreases drug resistance, and increases drug levels in the targeted tissue. This review presents the different types of LBNPs developed in recent years and their application in brain disorders.

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-Based Nanoparticles

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).

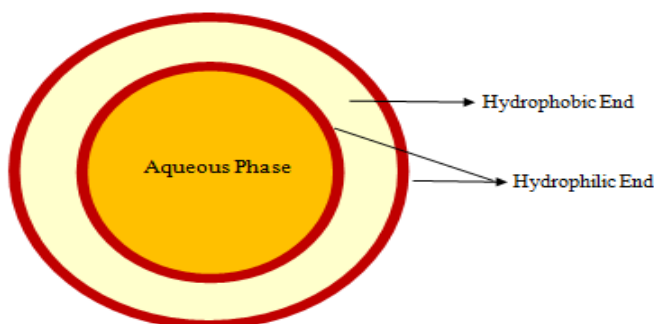


Figure 1: Liposome

Liposomes are mostly used in target brain therapy, due to the ability of 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:

Diioeoylsnglycero3phosphoethanolamine; DOTAP: Diioeoyl-3-trimethylammoniumpropane chloride; DMPC: 1,2-dimyristoylsnglycero-3-phosphocholine; DSPE: 1,2-distearoyl-snglycero-3-phosphoethanolamine-N[carboxy(polyethylene glycol)-2000];

DPPC: Dipalmitoylphosphatidylcholine ; EYPC: egg yolk phosphatidylcholine; PC-E: Phosphatidylcholine; PEG: Polyethylene Glycol; RGD: Arginine-lysine-aspartate; SPC: Soy phosphatidylcholine; 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).

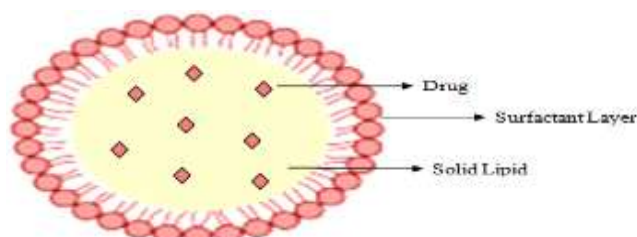


Figure 2: Solid nanoparticles

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	<i>Pueraria flavone</i>	More pronounced accumulation and 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 delivery system for psychiatric conditions	Yasira et al., 2014
10	CP, DMPC	High shear homogenisation and ultrasonic techniques	Camptothecine	Enhanced accumulation of camptothecine, Superior <i>in vitro</i> 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-sn-glycero-3-phosphoethanolamine-N-[carboxy(polyethylene glycol)-2000]; DDAB: dimethyldioctadecylammonium bromide; DMPC: 1,2-dimyristoyl-sn-glycero-3-phosphocholine; Lf: Lactoferrin; 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 tricaprilate, 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.

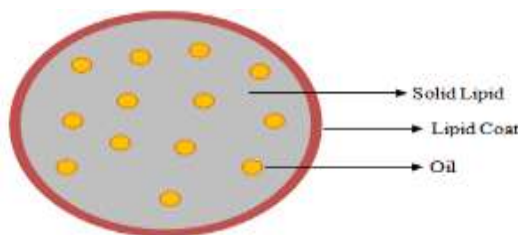


Figure 3: Nanostructured Lipid Carrier

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 triolein 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).

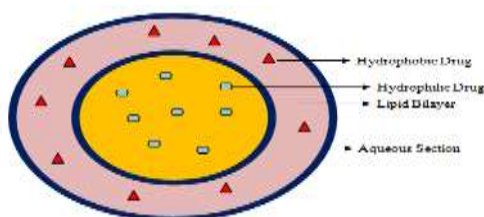


Figure 4: Niosome

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 drug molecules.

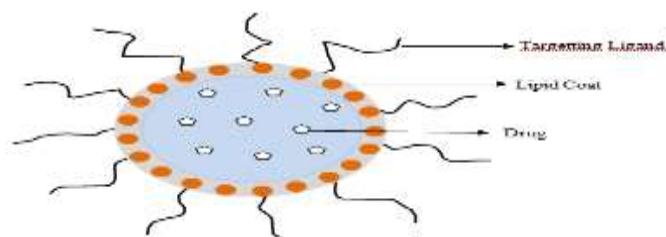


Figure 5: Lipid Nanocapsule

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 tumor 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 tumor. Cytotoxicity study revealed that internalisation of Fc-diOH-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 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 armamentarium of exogenous and nonimmunogenic ligands available for brain targeting. Finally, the consistency of the results served to validate a versatile screening method 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 by mixing 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 lipid nanocarriers and other polymeric nanoparticles. LPNs consist of two major parts: polymer and the lipid component. A typical LPN has a center shell structure. The polymeric core is used for loading various small molecule drugs and diagnostic agents and the lipid shell is used to confer stability and suitable biocompatibility (Wakaskar et. al., 2018).

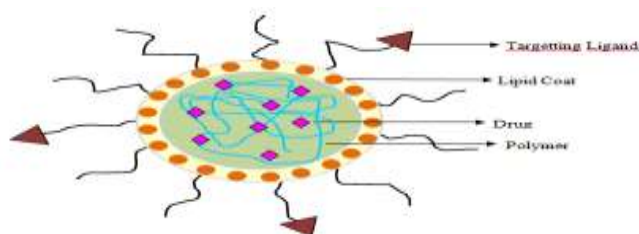


Figure 6: Lipid Polymer Hybrid Nanocarrier

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 delivery to the brain for the treatment of glioblastoma. The LPHN showed superior antitumor activity 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 of the principle of nanotechnology and colloidal lipid carrier systems has modernised the pattern of chemotherapeutic approaches in the treatment of numerous pathologies, especially in brain 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 outcomes as 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 needed to 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.

References

- [1] Abbas H., Refai H., Sayed N., 2018. Superparamagnetic Iron Oxide Loaded Lipid Nanocarriers Incorporated in Thermosensitive In Situ Gel for Magnetic Brain Targeting of Clonazepam. *Journal Pharmaceutical Science*. 107(8):2119-2127.
- [2] Ag D., Bongartz R., Dogan LE., 2014. Biofunctional quantum dots as fluorescence probe for cell-specific targeting. *Colloids Surf B Biointerfaces*. 114: 96-103.
- [3] Aparicio-Blanco, J., Romero, I. A., Male, D. K., Slowing, K., García-García, L., and Torres-Suárez, A. I., 2019. Cannabidiol Enhances the Passage of Lipid Nanocapsules across the Blood-Brain Barrier Both in Vitro and in Vivo. *Molecular Pharmaceutics*. 16(5), 1999–2010. [doi: 10.1021/acs.molpharmaceut.8b01344]
- [4] Bagul U, Pisal V, Solanki N., 2018. Current Status of Solid Lipid Nanoparticles: A Review. *Modern Applications of bioequivalence & bioavailability*. 3(4) : 1-2.
- [5] Bhargava S, Bhargava V., 2018. Surface Modified Solid Lipid Nanoparticles

- for the targeted delivery to brain: Management of HIV-1 Associated Dementia. *International Congress*. 880.
- [6] Brunn J, Larsen TB, Jolck RI., 2015. Investigation of enzyme-sensitive lipid nanoparticles for delivery of siRNA to blood–brain barrier. *International Journal of Nanomedicine*. 10: 5995-6008. [DOI: 10.2147/IJN.S87334]
 - [7] Chen Y, Pan L, Jiang M, Li D, Jin L., 2016. Nanostructured lipid carriers enhance the bioavailability and brain cancer inhibitory efficacy of curcumin both *in vitro* and *in vivo*. *Drug Delivery*. 23(4): 1383- 92.
 - [8] Das MK, Palei NN., 2011. Sorbitan ester niosomes for topical delivery of rofecoxib. *Indian J Exp Biol*. 49(6): 438-45.
 - [9] De, A., Venkatesh, N., Senthil, M., Sanapalli, B. K. R., Shanmugham, R., & Karri, V. V. S. R., 2018. Smart niosomes of temozolomide for enhancement of brain targeting. *Nanobiomedicine*. 5, 184954351880535. [doi: 10.1177/1849543518805355]
 - [10] El Maghraby, G.M., Williams, A.C., 2009. Vesicular systems for delivering conventional small organic molecules and larger macromolecules to and through human skin. *Expert Opin Drug Deliv*. 6(2): 149-63.
 - [11] Emami J., Rezazadeh M., Sadeghi H., Khadivar K., 2017. Development and optimisation of transferrin-conjugated nanostructured lipid carriers for brain delivery of paclitaxel using Box-Behnken design. *Pharm Dev Technol*. 22(3): 370-82
 - [12] Estabragh M.A.R.A., ZohrehHamidifar A., Abbas Pardakhty., 2018. Formulation of Rivastigmine Niosomes for Alzheimer Disease. *Pharmacy Updates*.
 - [13] Fatouh, A., Elshafeey, A., and Abdelbary, A., 2017. Intranasal agomelatine solid lipid nanoparticles to enhance brain delivery: formulation, optimisation and *in vivo* pharmacokinetics. *Drug Design, Development and Therapy*. Volume 11, 1815–1825. [doi: 10.2147/dddt.s102500]
 - [14] Gao, H., 2016. Progress and perspectives on targeting nanoparticles for brain drug delivery. *Acta Pharmaceutica Sinica B*. 6(4), 268–286. [doi: 10.1016/j.apsb.2016.05.013]
 - [15] Garcia-Pinel, B., Porras-Alcalá, C., Ortega-Rodríguez, A., Sarabia, F., Prados, J., Melguizo, C., and López-Romero, J. M., 2019. Lipid-Based Nanoparticles: Application and Recent Advances in Cancer Treatment. *Nanomaterials*. 9(4), 638. [doi: 10.3390/nano9040638]
 - [16] Hangargekar, S. R., Mohanty, P., and Jain, A., 2019. Solid Lipid Nanoparticles for Brain Targeting. *Journal of Drug Delivery and Therapeutics*, 9(6-s), 248–252. [doi: 10.22270/jddt.v9i6-s.3783]
 - [17] Huang FYJ, Lee TW, Chang CH., 2018. Evaluation of 188Relabeled PEGylated nanoliposome as a radionuclide therapeutic agent in an orthotopic glioma-bearing rat model. *Int J Nanomedicine*. 10: 463-73
 - [18] Ishii, T., Asai, T., Oyama, D., Agato, Y., Yasuda, N., Fukuta, T Oku, N., 2013. Treatment of cerebral ischemiareperfusion injury with PEGylated liposomes encapsulating FK506. *The FASEB Journal*. 27(4), 1362–1370. [doi: 10.1096/fj.12-221325]
 - [19] Küçükçürkmen, B., Devrim, B., Saka, O.M., Yilmaz, Ş., Arsoy, T., Bozkir, A., 2017. Co-delivery of pemetrexed and miR-21 antisense oligonucleotide by lipid-polymer hybrid nanoparticles and effects on glioblastoma cells. *Drug Dev Ind Pharm*. 43(1): 12-21.
 - [20] Kuo, Y.C., Cheng, S.J., 2016. Brain targeted delivery of carmustine using

- solid lipid nanoparticles modified with tamoxifen and lactoferrin for antitumor proliferation. *International Journal of Pharmaceutics*. 499: 10-19. [DOI: 10.1016/j.ijpharm.2015.12.054]
- [21] Lakkadwala, S., and Singh, J., 2019. Co-delivery of doxorubicin and erlotinib through liposomal nanoparticles for glioblastoma tumor regression using an in vitro brain tumor model. *Colloids and Surfaces B: Biointerfaces*. 173, 27–35. [doi: 10.1016/j.colsurfb.2018.09.047]
- [22] Lindqvist, A., Rip, J., Gaillard, P. J., Björkman, S., and Hammarlund-Udenaes, M. 2012. Enhanced Brain Delivery of the Opioid Peptide DAMGO in Glutathione PEGylated Liposomes: A Microdialysis Study. *Molecular Pharmaceutics*. 10(5), 1533–1541. [doi: 10.1021/mp300272a]
- [23] Martins, S.M., Sarmiento, B., Nunes, C., 2013. Brain targeting effect of camptothecin-loaded solid lipid nanoparticles in rat after intravenous administration. *European Journal of Pharmaceutics and Biopharmaceutics*. 85:488-502. [DOI: 10.1016/j.ejpb.2013.08.011]
- [24] Masserini, M., 2013. Nanoparticles for Brain Drug Delivery. *ISRN Biochemistry*. 2013, 1–18. [doi: 10.1155/2013/238428]
- [25] Mohanta, B. C., Dinda, S. C., Palei, N. N., and Deb, J., 2020. Solid Lipid Based Nano-particulate Formulations in Drug Targeting. *Role of Novel Drug Delivery Vehicles in Nanobiomedicine*. [doi: 10.5772/intechopen.88268]
- [26] Mohanta, B. C., Palei, N. N., Surendran, V., Dinda, S. C., Rajangam, J., Deb, J., and Sahoo, B. M., 2019. Lipid Based Nanoparticles: Current Strategies for Brain Tumor Targeting. *Current Nanomaterials*. 4(2), 84–100. [doi: 10.2174/2405461504666190510121911]
- [27] Nasiri, M., Azadi, A., Zanjani, M.R.S., and Hamidi, M., 2019. Indinavir-Loaded Nanostructured Lipid Carriers to Brain Drug Delivery: Optimisation, Characterisation and Neuropharmacokinetic Evaluation. *Current Drug Delivery*. 16(4), 341–354. [doi: 10.2174/1567201816666190123124429]
- [28] Neves A. R., Queiroz, J. F., Reis S., 2016. Braintargeted delivery of resveratrol using solid lipid nanoparticles functionalised with apolipoprotein E. *Journal of Nano biotechnology*. 14(27):1-11. [DOI: 10.1186/s12951-016-0177-x]
- [29] Orthmann, A., Zeisig, R., Süß, R., Lorenz, D., Lemm, M., and Fichtner, I., 2012. Treatment of Experimental Brain Metastasis with MTO-Liposomes: Impact of Fluidity and LRP-Targeting on the Therapeutic Result. *Pharmaceutical Research*. 29(7), 1949–1959. [doi: 10.1007/s11095-012-0723-7]
- [30] Papachristodoulou, A., Signorell, R.D., Werner, B., Brambilla, D., Luciani, P., Cavusoglu, M., Leroux, J.-C., 2019. Chemotherapy sensitisation of glioblastoma by focused ultrasound-mediated delivery of therapeutic liposomes. *Journal of Controlled Release*. 295, 130–139. [doi: 10.1016/j.jconrel.2018.12.009]
- [31] Pardridge, W.M., 2007. Drug targeting to the brain. *Pharm Res*. 24:1733–44.
- [32] Qu, J., Zhang, L., Chen, Z., 2016. Nanostructured lipid carriers, solid lipid nanoparticles, and polymeric nanoparticles: which kind of drug delivery system is better for glioblastoma chemotherapy. *Drug Delivery*. 23(9): 3408-16.
- [33] Ravouru, N., Kondreddy, P., Korakanchi, D., and M., H. 2013. Formulation and Evaluation of Niosomal Nasal Drug Delivery System of Folic Acid for Brain Targeting. *Current Drug Discovery Technologies*. 10(4), 270–282. [doi: 10.2174/15701638113109990031]
- [34] Rodrigues, B.D.S., Oue, H., Banerjee, A., Kanekiyo, T., and Singh, J., 2018.

- Dual functionalised liposome-mediated gene delivery across triple co-culture blood brain barrier model and specific in vivo neuronal transfection. *Journal of Controlled Release*. 286, 264–278. [doi: 10.1016/j.jconrel.2018.07.043]
- [35] Roger, M., Clavreul, A., Huynh, N.T., 2012. Ferrociphenol lipid nanocapsule delivery by mesenchymal stromal cells in brain tumor therapy. *Int J Pharm*. 423(1): 63-8.
- [36] Rotman, M., Welling, M.M., Bunschoten, A., Backer, M.E.D., Rip, J., Nabuurs, R. J., Weerd, L.V.D., 2015. Enhanced glutathione PEGylated liposomal brain delivery of an anti-amyloid single domain antibody fragment in a mouse model for Alzheimers disease. *Journal of Controlled Release*. 203, 40–50. [doi: 10.1016/j.jconrel.2015.02.012]
- [37] Sita, V., Jadhav, D., and Vavia, P., 2020. Niosomes for nose-to-brain delivery of bromocriptine: Formulation development, efficacy evaluation and toxicity profiling. *Journal of Drug Delivery Science and Technology*. 58, 101791. [doi: 10.1016/j.jddst.2020.101791]
- [38] Sivadasu, P., Gowda, D.V., Subramani, N.K., Vishweshwaraiah, B.M., Shivanna, S., and Hatna, S., 2019. Direct Brain Targeted Nanostructured Lipid Carriers for Sustained Release of Schizophrenic Drug: Formulation, Characterisation and Pharmacokinetic Studies. *Indian Journal of Pharmaceutical Education and Research*. 54(1), 73–84. [doi: 10.5530/ijper.54.1.9]
- [39] Song, S., Mao, G., Du, J., and Zhu, X., 2015. Novel RGD containing, temozolomide-loading nanostructured lipid carriers for glioblastoma multiforme chemotherapy. *Drug Delivery*. 23(4), 1404–1408. [doi: 10.3109/10717544.2015.1064186]
- [40] Teleanu, D., Chircov, C., Grumezescu, A., Volceanov, A., and Teleanu, R., 2018. Blood-Brain Delivery Methods Using Nanotechnology. *Pharmaceutics*. 10(4), 269. [doi: 10.3390/pharmaceutics10040269]
- [41] Wakaskar, R.R., 2018. General overview of lipid-polymer hybrid nanoparticles, dendrimers, micelles, liposomes, spongosomes and cubosomes. *J Drug Target*. 26(4): 311-8.
- [42] Wang, J.X., Sun, X., Zhang, Z.R., 2002. Enhanced brain targeting by synthesis of 3',5'-dioctanoyl-5- fluoro-2'-deoxyuridine and incorporation into solid lipid nanoparticles. *European Journal of. Pharmaceutics and Biopharmaceutics*. 54 (3) : 285– 290. [doi: 10.1016/s0939-6411(02)00083-8]
- [43] Wang, Z., Zhao, Y., Jiang, Y., Lv, W., Wu, L., Wang, B., and Xin, H., 2015. Enhanced anti-ischemic stroke of ZL006 by T7-conjugated PEGylated liposomes drug delivery system. *Scientific Reports*. 5(1). [doi: 10.1038/srep12651]
- [44] Wolburg, H., Noell, S., Fallier-Becker, P., Mack, A.F., Wolburg-Buchholz, K., 2012. The disturbed blood–brain barrier in human glioblastoma. *Mol Aspects Med*. 33:579–89
- [45] Wu, M., Fan, Y., Lv, S., Xiao, B., Ye, M., Zhu, X., 2016. Vincristine and temozolomide combined chemotherapy for the treatment of glioma: a comparison of solid lipid nanoparticles and nanostructured lipid carriers for dual drugs delivery. *Drug Deliv*. 23(8): 2720-5.
- [46] Xia, C.F., Boado, R.J., Zhang, Y., Chu, C., and Pardridge, W.M., (2008). Intravenous glial-derived neurotrophic factor gene therapy of experimental Parkinsons disease with Trojan horse liposomes and a tyrosine hydroxylase

- promoter. *The Journal of Gene Medicine*. 10(3), 306–315. [doi: 10.1002/jgm.1152]
- [47] Yasira, B., 2014. Solid lipid nanoparticles for nose to brain delivery of haloperidol: in vitro drug release and pharmacokinetics evaluation, *Acta Pharmaceutica Sinica B*. 4(6):454–463.
- [48] Yingchoncharoen, P., Kalinowski, D.S., Richardson, D.R., 2016. Lipid-Based Drug Delivery Systems in Cancer Therapy: What Is Available and What Is Yet to Come. *Pharmacol. Rev.* 68, 701–787.