Section A-Research paper
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NANOSTRUCTURED LIPID CARRIERS AS BRAIN-TARGETED DRUG DELIVERY SYSTEMS

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Abstract

The Blood Brain Barrier (BBB) poses a significant obstacle to medication transport to the CNS because of the compressed endothelial interconnections of capillaries at its interface. Many delivery approaches have been tried in an effort to develop a brain-targeted delivery system with a desirable combination of properties, with BBB penetration being among the most crucial. Because of their diminutive size, NLCs may cross the BBB passively, releasing their contents gradually over time and protecting the encapsulated medication from breakdown while it travels to the targeted site. Furthermore, the Nano carrier's surface can be functionalized to create a targeted delivery system. Drugs trapped in NLCs may be delivered in a variety of methods, including intranasally, intravenously, or orally, and the process is completely non-invasive. This review discusses the use of NLCs through different routes of administration for the treatment of neurological diseases.

Keywords: *Nanostructured lipid carriers (NLCs), brain targeting, Blood-brain-barrier, intranasal delivery, oral delivery, intravenous delivery.*

1. Introduction

Delivering medicines to the CNS presents unique challenges, which have made it difficult to synthesize nanoparticles for use in treating brain illnesses (Tapeinos et al., 2017). A variety of delivery approaches have been implemented with the ultimate goal of developing a system that crosses the BBB while still retaining desirable properties such as higher drug-loading efficiency, bio-compatibility and stealth. To this end, researchers have investigated inorganic and organic nanoparticles that have been modified with targeting groups and/or encased with exterior layers of different biomimetic substances (Cui et al., 2016; Stater et al., 2021). Nanostructures made of lipids, such as liposomes (Lai et al., 2013; Sonkar et al., 2021), SLNs and NLCs (Jnaidi et al., 2020), lipoplexes (de Boer et al., 2007), lipoproteins (Ma et al., 2018; Song et al., 2016), polymeric nanoparticles (Raman et al., 2020; Costantino and Boraschi, 2012; Patel et al., 2012; Kempe and Nicolazzo, 2021; Tosi et al., 2008; O Elzoghby et al., 2016), polymeric micelles (Kotta et al., 2022), dendrimers (Zhu et al., 2019; Beg et al., 2011; Gauro et al., 2021), and inorganic nanoparticles such as iron oxide (Qiao et al., 2023), ceria

(Choi and Kim, 2020; Kwon et al., 2016), gold (Cheng et al., 2011; Guerrero et al., 2010) and quantum dots (Calabrese et al., 2021), have received the greatest attention for use in drug delivery to the central nervous system. The aforementioned systems each come with their own set of benefits and drawbacks.

The Blood Brain Barrier (BBB) limits medication entry into the brain by closing off the capillary endothelial interconnections (Mansor et al., 2019), making drug administration to the CNS a difficult undertaking. While only extremely lipophilic drugs are able to cross the barrier, essential nutrients are actively transported into the cell. The technique for medication distribution by rupture of the BBB is intrusive and causes discomfort. Additionally, more intrusive approaches, like the intrathecal injection of medicine directly, are not always feasible for patients who need long-term therapy. Substitutes for this invasive method include intranasal (IN) drug delivery, nanoparticles, prodrugs, and the utilization of chimeric peptides (vector mediated), which can still deliver the medicine to the CNS, but under far more manageable conditions (Bodor and Buchwald, 2003). Nano carriers whose surfaces have been modified have been found to be taken up more efficiently by the BBB (Salatin et al., 2015).

Nanostructured lipid carriers (NLCs) are a type of lipid nanoparticles with a solid lipid core as the distinguishing feature (Yoon et al., 2013). The matrix of the Nano lipid particles thus formed has a lower melting point than the initial solid lipid, but remains solid at body temperature. Various NLCs, including imperfect, amorphous, and multiple types, can be made through various production techniques and by adjusting the lipid blend composition (Battaglia and Gallarate, 2012; A Attama, 2011). NLCs improve both drug release and drug loading capacity because they generate a less organized lipid matrix. According to research Haque et al. (2012), NLC may block the p-gp efflux pump, allowing for a greater amount of the medication in the brain and the possibility of it circulating for a longer duration. Due to their diminutive size, nanoparticles may passively diffuse across the blood-brain barrier (BBB) and into the brain, where they can shield the encapsulated medicine from disintegration and gently deliver it to the targeted site. Furthermore, the Nano carrier's surface can be functionalized to create a targeted delivery system

Emami et al. (2017) found that transferrin-coated NLCs for brain delivery of paclitaxel (Tf-PTX-NLCs) had better cytotoxic activity than free drug, suggesting that Tf-PTX-NLCs might be used as a delivery method in brain tumors. The study of Arduino et al., released recently, was rather intriguing. In order to facilitate the removal of beta-amyloid from the brain tissue, they engineered NLCs containing a chemical (MC111) that may stimulate the transcription of two transporters generated at the surface of the cerebral endothelium: P-gP and BCRP (Arduino et al., 2020). In this research, transferrin was used to functionalize the Nano systems. Interestingly, the biological experiments conducted on BBB-forming hCMEC/D3 cell cultures showed that treatment with NLC-MC111 increased the activity of both transporters, with the rise being greatest for Tf-NLC-MC111. This finding confirmed that the modified Nano systems not only penetrated the barrier model, but also increased P-gP and BCRP activity by delivering a higher concentration of medication within the cells (Arduino et

al., 2020). When compared to quercetin-loaded SLNs, quercetin-loaded NLCs significantly increased relative bioavailability (roughly 6 folds), biological residence (roughly 2.5 times), and significantly slowed the drug clearance (roughly 6 folds). However, both nanoparticles successfully delivered a significant amount of the drug to the brain. It has been shown that NLCs significantly increase drug absorption in the brain (Kumar et al., 2016). For the purpose of repairing post-ischemic brain damage, Wu et al. have adapted these Nano systems to transport compounds. Through the use of the transferrin receptor monoclonal antibody OX26, Salvianolic Acid and Baicalin-carrying NLCs (OX26-BA/Sal BNLC) were successfully established. According to the findings of an in vitro investigation (Wu et al., 2019), NLC-based delivery method facilitates the release of encapsulated drugs that have a reparative/improvement impact on the health of treated neural cells. Carbamazepine-loaded NLC was studied for its anticonvulsant and anxiolytic effects in an effort to determine its efficacy in brain delivery (Khan et al., 2020). Curcumin-loaded NLCs that were modified with transferrin were effectively generated and transported across the BBB to the brain. Curcumin's ability to cross the BBB was confirmed to be increased by a factor of 1.5. The attachment of transferrin to the outer layer of the NLCs makes them a good candidate for curcumin brain administration, since it protects the integrated curcumin and directs it to the brain (Neves et al., 2021). Two protease-stable D-peptides, D8 and RI-VAP (Dual NLCs), were incorporated into NLCs to provide a brain-targeted delivery method. Bortezomib (BTZ)-loaded Dual NLCs showed the greatest therapeutic efficacy, as shown by increased cytotoxicity and apoptosis in vitro, as well as increased survival rate and effective anti-glioma activity in mice with intracranial glioma. The designed targeting system successfully delivered BTZ to glioma cells, demonstrating its promise for cutting-edge brain cancer therapy with ensuring therapeutic results (Farshbaf et al., 2022). Commonly used routes of NLC administration are depicted in Figure 1.

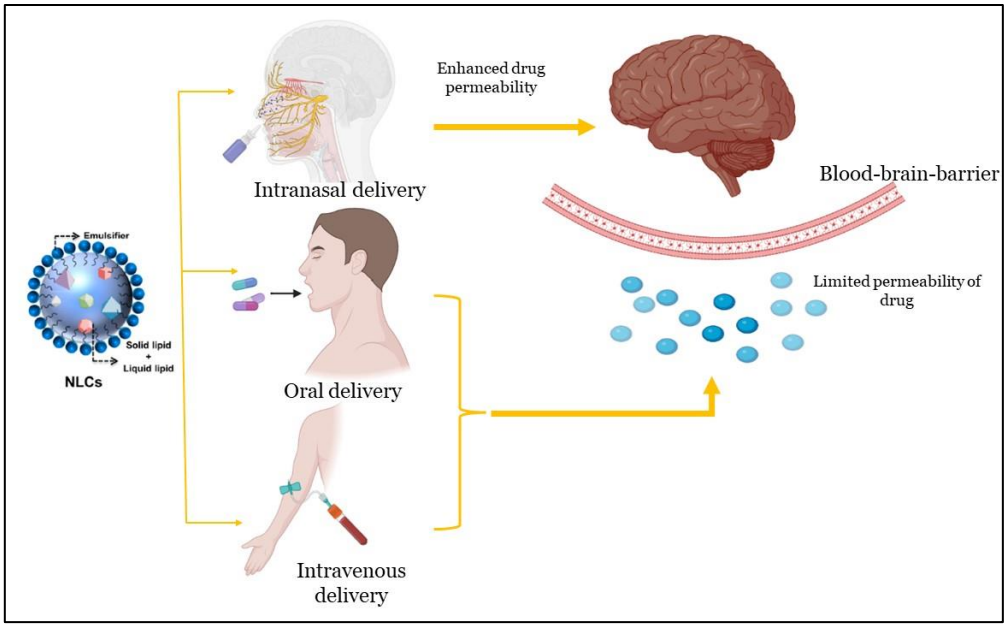

Figure 1: NLCs in the treatment of neurological illnesses by various routes of administrations

2. Intranasal Route

Drugs used orally or intravenously for central nervous system problems must be dosed repeatedly, which increases the drug's exposure to the body and may have negative effects on the organs. To avoid these side effects, intranasal medication administration is increasingly being used to carry drugs directly to the brain through the olfactory or trigeminal nerve pathways (Figure 2) (Selvaraj et al., 2018). For treating epilepsy via the IN route, scientists created NLCs loaded with lamotrigine (LMT) that consistently released the medication at zero order. Epilepsy was controlled more effectively with IN-administered LMT-NLCs, according to pharmacodynamic experiments in rats subjected to Maximal Electro Shock (MES) (Alam et al., 2015). Excellent brain uptake of drug was confirmed using ex vivo permeation tests using goat nasal mucosa. Effective medication delivery to the brain through the IN route was shown for the treatment of HIV infection in the central nervous system using efavirenz (EFV), a powerful non-nucleoside reverse transcriptase inhibitor (non-NRTI) synthesized as NLC (Pokharkar et al., 2017). Upon intranasal injection, chitosan-coated NLCs were shown to be efficiently delivered to the brain in a biodistribution investigation (Gartziandia et al., 2015). Intranasal delivery of clozapine-loaded NLCs showed a 6.15-fold improvement in relative bioavailability by avoiding hepatic first-pass effect and crossing the BBB (Patel et al., 2021). After intranasal delivery, the brain levels of lurasidone hydrochloride-loaded NLC was found to be twice as high as that of the drug solution (Jazuli et al., 2019). Ketoconazole (keto)-NLCs have dramatically improved antifungal effectiveness on C. neoformans in vivo across a wide range of growth settings. The NLCs have superior abilities to colonize tissues. Imaging studies in animals have shown that NLCs may cross the blood-brain barrier (BBB) and reach brain tissues through the olfactory bulb area after intranasal delivery. Oleuropein-loaded NLC had greater absolute bioavailability in the brain when supplied through the intranasal route than when given intravenously (Palagati et al., 2019).

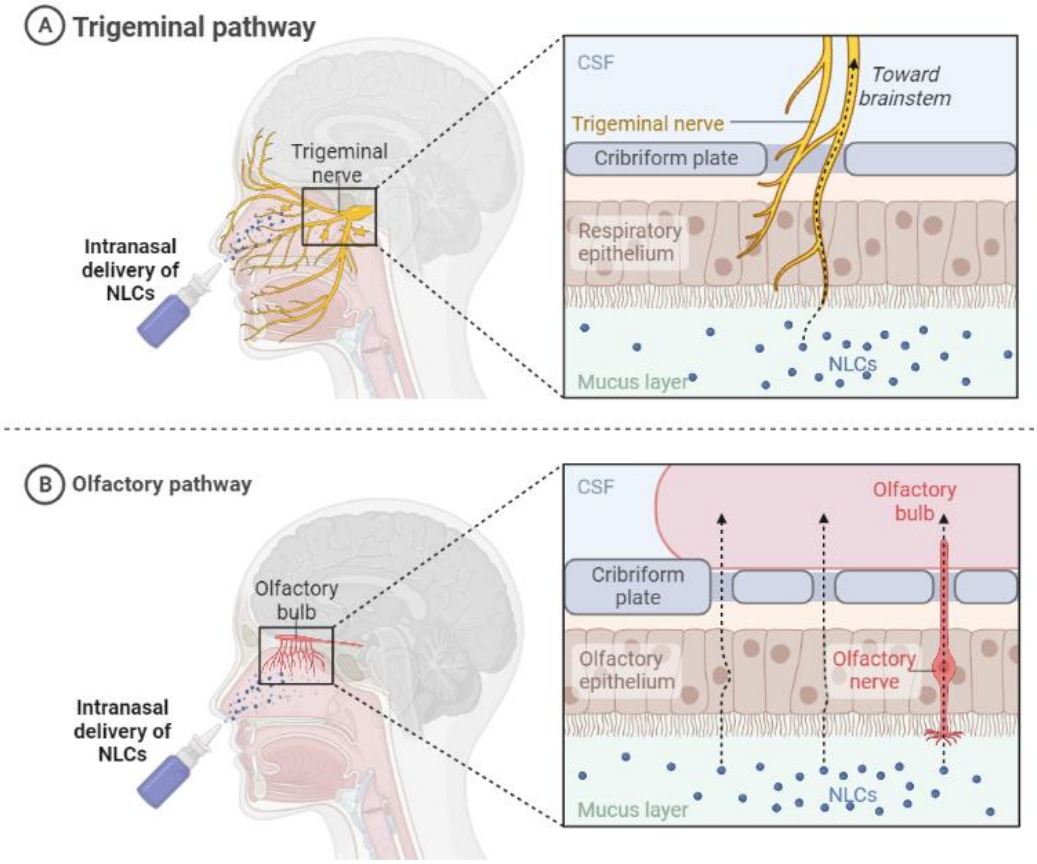

Figure 2: Direct pathways for intranasal delivery of drug-loaded NLCs

The current standard of care for Parkinson's disease is dopamine replacement medication for the management of motor dysfunction (Gonzalez-Latapi et al., 2020). Eventually, when the disease worsens, this therapy will no longer be able to alleviate symptoms. So, treating neurodegeneration with growth factors is an exciting new therapeutic avenue. Cell-penetrating peptide TAT was used to modify the surface of NLC-formulated glial-derived neurotropic factor (GDNF). Intranasal injection in a mouse model of MPTP-induced neurodegeneration allowed researchers to assess its neuroprotective and brain cell repair capabilities (Hernando et al., 2018). The acetylcholine esterase enzyme may be inhibited by employing rivastigmine-loaded NLCs when they were administered intravenously (IV) using a gellan gum-based in situ gelling technique. For the treatment of Alzheimer's disease, this is a helpful finding (Wavikar & Vavia, 2015). Alam et al. looked into the efficacy of duloxetine-NLCs as an intranasal therapy for depression. It was found that duloxetine-NLCs had permeabilities 2.5 times higher than drug solution (Alam et al., 2013). Duloxetine-NLCs were shown to have a greater concentration of drug in the brain. Studies of the pharmacokinetics and brain absorption of artemether-loaded NLCs have shown that a greater concentration of the drug is detected in the brain when the medication is administered intranasally (Jain et al., 2015). Valproic acid (VPA)-loaded NLCs were intranasally administered to animal models of MES-induced seizures. Brain and plasma drug concentrations were measured, and the results revealed that intranasal delivery of NLCs of

VPA offered significantly superior defense against the MES seizure relative to the control group (Eskandari et al., 2011). In addition, NLCs loaded with temozolomide (TMZ) have been created for intranasal delivery to GBM. The considerable effectiveness of intranasal delivery of NLCs has been proven by in vivo experiments showing enhanced brain levels of TMZ-NLCs than free TMZ (Khan et al., 2016). CLSM pictures of brain cryosections tagged with caumarin-6 NLCs demonstrate the persistent brain localisation and buildup of NLCs after NLCs-based intranasal administration of tenofovir disoproxil fumerate. According to the findings, the engineered NLCs may be able to transfer TDF to the brain for an extended period of time, making them a promising therapy for NeuroAIDS (Sarma et al., 2020).

Table 1: Studies on intranasally administered drug-loaded NLCs

Drug	Targeted disease	Subjects	Outcome	References
Lamotrigine	Epilepsy	Maximal Electro Shock induced animals	NLC has improved drug permeability.	Alam et al., 2015
Efavirenz	HIV	Male Wistar rats.	There were no hazardous and morbid effects.	Pokharkar et al., 2017
Chitosan	CNS disorders	Athymic nude female mice	Effective transport of the drug-loaded particles to the brain	Gartziandia et al., 2015
Clozapine	Schizophrenia	Female albino mice	A 6.15-fold improvement in relative bioavailability was achieved by avoiding first-pass effect in the liver and crossing the BBB.	Patel et al., 2021
Lurasidone hydrochloride	Schizophrenia	Albino Wistar rats	There was a twofold rise in brain levels of drug.	Jazuli et al., 2019
Ketoconazole	Meningoencephalitis	Six- to eight-week-old female C57BL/6 mice	Limit Substantial Growth and invasion of C. neoformans in the brain	Du et al., 2019
Glial derived neurotropic factor	PD	MPTP mouse model	Capability of protecting and restoring neural cells	Hernando et al., 2018
Rivastigmine	Alzheimer's disease	Indian sheep	Drug penetration improved by a factor of 1.6	Wavikar and

				Vavia, 2015
Duloxetine	Depression	Wistar rats	Greater permeation than medication solution by a factor of 2.5	Alam et al., 2013
Artemether	Cerebral malaria	Male Wistar rats	The brain was shown to have an increased drug content.	Jain et al., 2015
Valproic acid	Epilepsy	Rat models of maximal electroshock seizures	Higher concentrations of drug in brain tissue relative to plasma	Eskandari et al., 2011
Temozolomide	GBM	Healthy Wistar rats	Accumulation of TMZ-NLCs in the brain is enhanced.	Khan et al., 2016
Tenofovir disoproxil fumerate	Neurological complications of AIDS	Albino Wistar rats	A persistent buildup of NLCs in brain tissue	Sarma et al., 2020

3. Intravenous Route

Treatment of central nervous system (CNS) disorders with oral drugs might lead to undesirable physiological side effects (Salvi and Pawar, 2019; Tiwari et al., 2012; Misra et al., 2003). To counteract these drawbacks, a parenteral NLC treatment has been devised that preferentially affects the brain while avoiding other organs. Esposito et al. (2012) found that NLCs made in the presence of Pluronic F68 acted as stealth carriers, improving brain-targeted delivery of bromocriptine. Agrawal et al. (2020) explain that this improvement is due to the gradual drug release, endocytosis through unique endogenous transporters, and loosening of the closed junction. The beneficial effects of bromocriptine NLCs on motor impairments in 6-hydroxydopamine hemilesioned rats are determined using two behavioral assessments specific for akinesia (bar test) or akinesia/bradykinesia (drug test). Compared to the control solution, NLCs have an extended duration (5 h) in reducing immobility time, while bromocriptine in both solutions reduces immobility time. This demonstrates that NLCs prolong the half-life of the medication, hence providing sustained therapeutic effectiveness. Researchers have established artemether-lumefantrine as an additive intravenous NLC therapy that selectively targets CNS-residing parasitic malarial organisms upon daily administration for a period of four days, resulting in a full recovery of cerebral malaria (CM) symptoms and an impressive survival rate in animals with minimal organ toxicity (Prabhu et

al., 2016). Vanka et al. found a similar result when they injected artemether NLC intraperitoneally: up to 60% survival rate and improved activity against parasites associated with malaria (Vanka et al., 2018). After incorporating NLCs into baicalein, Tsai et al. looked into its ability to be targeted specifically to the brain via intravenous injection (Tsai et al., 2012). Baicalein treatment resulted in significantly larger plasma levels and a longer half-life in NLCs compared to the control. Baicalein was shown to accumulate 7.5 and 4.7 times more in the NLCs' cerebral cortex and brain stem, correspondingly, than in the control. The olfactory system, thalamus, striatum, and hippocampus also showed greater accumulation (by a ratio of 2-3). Intravenous administration of apomorphine NLCs was studied to see whether it prolonged the drug's brain targeting and deposition (Hsu et al., 2010). NLCs were able to effectively encapsulate 60% of the apomorphine base form. Rat brain sections fluorescence imaged in real-time bioluminescence showed that NLCs may be targeted via specific cerebral arteries.

Table 2: Studies on intravenously administered drug-loaded NLCs

Drug	Targeted disease	Subject	Outcome	References
Apomorphine	PD	Male Sprague Dawley rats	The ability to accumulate in the brain and maintain brain targeting over time was enhanced.	Hsu et al., 2010
Artemether	CM	CM induced mice	Improved lifespan by 60% and more effective treatment of malaria parasites	Vanka et al., 2018
Artemether-lumefantrine combination	Cerebral malaria (CM)	Plasmodium berghei-infected mice	Complete remission of symptoms and very high success rates	Prabhu et al., 2016
Baicalein	CNS disorders (Ischemic strokes)	Male Wistar albino rats	Brain stem and cortex baicalein levels increased by 7.5 and 4.7 times, respectively.	Tsai et al., 2012
Bromocriptine	Parkinson's disease	Animal model for Parkinson's disease	Extend the duration of the drug's therapeutic effects by increasing its half-life.	Agrawal et al., 2020
Curcumin	AD	AD model of rats	Effectively cross the blood-brain barrier and deposit there	Meng et al., 2015
Curcumin	AD	Rat model or AD	Successful medication administration and enhanced therapeutic action	Sadegh et al., 2019

Nimodipine	Strokes	BALB/c nude mice	Transmit nimodipine to the brain through penetrating the BBB.	Zhao et al., 2018

It has been shown that curcumin-loaded NLCs may successfully cross the blood-brain barrier (BBB) and aggregate predominantly in the brain (Meng et al., 2015). To combat this, scientists created lactoferrin-modified NLCs (Lf-NLC). Nanoparticles containing nimodipine loaded by Lf-NLC exhibited good loading efficiency and limited size dispersion. By crossing the BBB, nimodipine might be delivered to brain tissue through Lf-NLC (Zhao et al., 2018). Curcumin-containing NLCs were developed and evaluated in an Alzheimer's disease rat model. This study's findings show that Cur-NLC, when administered using the right delivery system, improves spatial memory and reduces beta-amyloid aggregates in the hippocampus and other brain regions, demonstrating that the drug is able to penetrate to the nerve cells and exert its therapeutic effects. According to these findings, the medicine is able to travel to its target location attributable to the formulation design used, hence avoiding the difficulties often connected with treating the brain (Sadegh et al., 2019).

4. Oral Route

Most pharmaceuticals on the market suffer from low bioavailability, prompting several research teams to focus on developing effective oral delivery methods (Poonia et al., 2016). It has been shown that encapsulating bioactives inside NLCs improves their therapeutic efficacy and the release of the bioactive from the NLCs over a longer period of time, leading to better pharmacokinetic characteristics (Khosa et al., 2018).

Table 3: Studies on orally administered drug-loaded NLCs

Drug	Targeted disease	Subjects	Outcome	References
Atazanavir	Neurological complications of AIDS	Adult albino Wistar rats	Increased brain bioavailability by a factor of 4	Khan et al., 2020
Dimethyl fumarate	Multiple sclerosis.	Adult wistar rats	There was a notable increase in oral and brain availability.	Kumar et al., 2017
Paliperidone	Psychosis	Rodent's model of ketamine-induced psychosis	Higher Brain Drug Concentration	Rehman et al., 2022
Temazepam	-	Sprague–Dawley rats	Specific brain-binding affinity	E. Eleraky et al., 2020

The oral administration of temazepam-NLCs revealed a striking brain-targeting specificity (E. Eleraky et al., 2020). One of the main problems with using atazanavir (ATZ) for the treatment of NeuroAIDS is that, when taken orally, it has low brain bioavailability. The advantage of the NLC formulations over the drug solution was shown by pharmacokinetic experiments, which showed a 2.75-fold increase in Cmax in the brain and a 4-fold enhancement of brain bioavailability (Khan et al., 2020). Antipsychotic performance was optimized by developing paliperidone-loaded NLCs (PPD-NLC). When comparing the drug suspension and the oral administration of PPD-NLC, Rehman et al. (2022) found that the NLC treatment resulted in greater brain levels of the drug at all time periods. Dimethyl fumarate was conjugated with NLCs, which increased its oral bioavailability by 4.09 times and its brain availability greatly compared to the free medication (Kumar et al., 2017). The mechanism of enhancement of poorly water-soluble (PWS) drugs is shown in Figure 3.

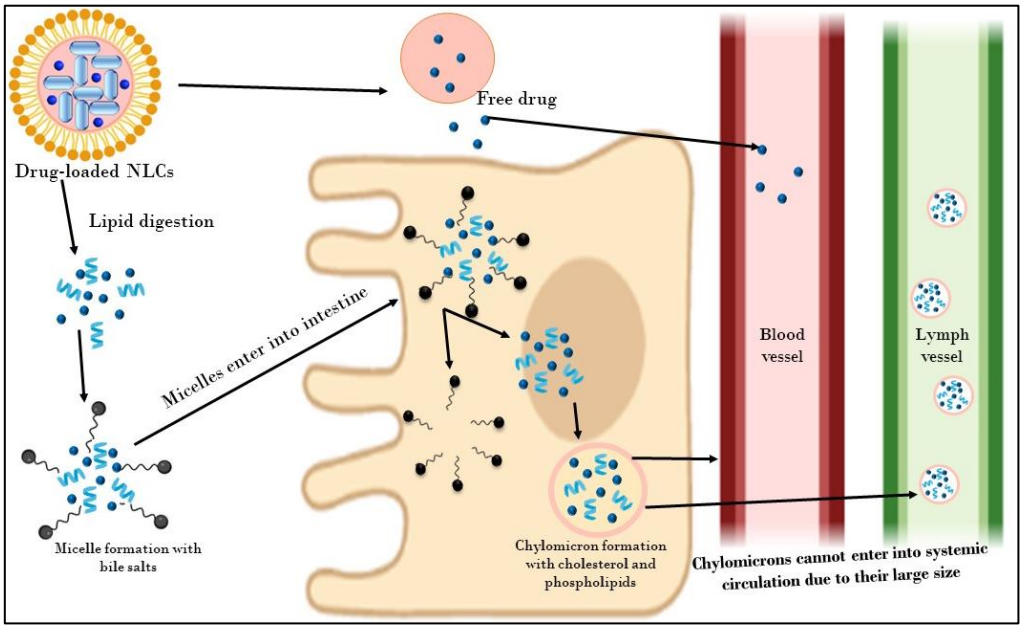

Figure 3: Enhancement of oral bioavailability of PWS drugs by NLCs' mechanism.

5. Conclusion:

Encasing medications in nanocarriers may improve their capacity to cross the blood-brain barrier and reach the brain. Although the BBB is a challenging barrier, NLCs can cross it via receptor-mediated transcytosis, which allows them to enter the brain. Multiple routes of administration are possible for drugs carried by nanocarriers, and the approach is non-invasive. The most common ways that NLCs administer drugs are through intravenous injection and intranasal delivery. In addition, the advent of NLC formulation provides new possibilities for the creation of novel approaches to the difficulty of orally administering poorly-water soluble (PWS) compounds. There has been clear progress in NLCs throughout time, as shown by the many studies included in this paper. In conclusion, NLCs are the most

promising area for neurodegenerative disease research because of their high drug load, stability, biocompatibility, and capacity to cross the BBB.

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