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Review Article

# Drug delivery to the brain – lipid nanoparticles-based approach

Viliana Gugleva[1], Velichka Andonova[1]

1 *Department of Pharmaceutical Technologies, Faculty of Pharmacy, Medical University of Varna, Varna, Bulgaria*

Corresponding author: Viliana Gugleva (viliana.gugleva@gmail.com)

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## Abstract

The complex structure of the human brain defines it as one of the most inaccessible organs in terms of drug delivery. The blood-brain barrier (BBB) represents a microvascular network involved in transporting substances between the blood and the central nervous system (CNS) – enabling the entry of nutrients and simultaneously restricting the influx of pathogens and toxins. However, its role as a protective shield for CNS also restricts drug access to the brain. Since many drugs cannot cross the BBB due to unsuitable physicochemical characteristics (i.e., high molecular weight, aqueous solubility, etc.), different technological strategies have been developed to ensure sufficient drug bioavailability. Among these, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are promising approaches thanks to their lipid nature, facilitating their brain uptake, small sizes, and the possibilities for subsequent functionalization to achieve targeted delivery. The review focuses on applying SLNs and NLCs as nanocarriers for brain delivery, outlining the physiological factors of BBB and the physicochemical characteristics of nanocarriers influencing this process. Recent advances in this area have also been summarized.

## Keywords

blood-brain barrier, ligands, nanostructured lipid carriers, receptors-mediated transcytosis, solid lipid nanoparticles

## Introduction

The human brain is considered one of the most challenging therapeutic areas for drug delivery due to its protective physiological barriers (blood-brain and blood-cerebrospinal fluid barrier) (Abbot et al. 2010). Hereof, still, nowadays, most treatments for neurodegenerative diseases (Parkinson's/Alzheimer's disease, etc.) generally result in symptom relief (Poddar et al. 2020). In the case of brain neoplasms, the therapeutic outcomes are even poorer (Miller et al. 2021). The blood-brain barrier is the primary factor restricting drug transport to the brain – approximately 98% of small molecules and almost 100% of drugs cannot reach the brain parenchyma (Pardridge 2003). Structurally, it comprises endothelial cells, astrocytes, and pericytes (Stone et al. 2019). The tight junctions and adherens junctions between the brain capillary endothelial cells are mainly responsible for its diffusion barrier role, low permeability, and high electrical resistance (≈ 500–600 higher than other body parts) (Alam et al. 2010). In this context, research strategies are constantly evolving to find a feasible approach to circumvent the BBB, ideally via physiological pathway mechanisms without compromising its integrity, and to deliver drugs to the brain parenchyma, thereby providing safe and effective treatment for a variety of CNS disorders. The main strategies to achieve these goals can be broadly classified into invasive and non-invasive approaches (Yasir et al. 2016). Through invasive methods, the drugs can reach the brain either directly, via temporary disruption of the

BBB using hyperosmotic solutions or ultrasound, or by intra-cerebral/ventricular/thecal delivery (Bahadur et al. 2020). However, these strategies are associated with low patient compliance, technical difficulties, and, last but not least, risk of exposure of the brain to toxins or occurrence of neuropathological changes in case of transient BBB disruption (Alam et al. 2010). Great research interest provokes the non-invasive approaches, which use either an alternative route to reach the CNS – as in the case of the nose-to-brain delivery via the olfactory and trigeminal nerve pathways, or different techniques enabling drugs` transport across the BBB (Hanson and Frey 2008; Bellettato and Scarpa 2018). The most applied strategies may be classified as 1) ***physiological approach*** **–** using the endogenous BBB transport systems; 2) ***chemical approach*** – increasing drug lipid solubility, prodrug bioconversion, development of chimeric peptides, cationic proteins; 3) ***biological approach*** – drug conjugation with antibodies, use of molecular "Trojan horses" (transport vectors able to cross the BBB); 4) ***colloidal carrier systems approach*** – elaboration of novel nanoscale drug delivery systems such as liposomes, nanosuspensions, solid lipid nanoparticles, polymeric/inorganic nanoparticles, etc. (Pardridge 2006; Nagpal et al. 2013; Yasir et al. 2016).

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are among the most exploited platforms for brain delivery due to their superior safety profile in terms of potential cytotoxicity, biodegradability, or biocompatibility compared, for instance, to the polymeric or inorganic counterparts (Kaur et al. 2008). Furthermore, they are characterized by high drug-loading capability, controlled drug release, and scale-up feasibility. In addition to the excellent tolerability, their main structural constituents (lipids, in solid-state at room/physiological temperature in SLNs, and a mixture of solid and liquid lipids in case of NLCs) provide them the possibility to cross the BBB (Neves et al. 2015). Undoubtedly, the latter is also highly dependent on the physicochemical characteristics of the nanocarriers, primarily by their size, surface charge, shape, and, last but not least, their surface modification. Therefore, the functionalization of lipid nanoparticles (LNPs) with different ligands (e.g., proteins, peptides, antibodies, etc.) is a prerequisite for further improvement of their brain target selectivity and therapeutic outcomes. In this regard, the impact of the physicochemical and surface properties of LNPs, along with the potential transport mechanisms and the specific characteristics of the target area – BBB's structure are discussed in the paper. The review also summarizes current studies exploiting SLNs and NLCs as brain drug delivery systems.

## Blood-brain barrier – structure and transport mechanisms

The blood-brain barrier plays a significant role in maintaining homeostasis in the CNS by controlling the transport of substances between the bloodstream and the brain (Xiao et al. 2020). Besides as a physical barrier, protecting the neuronal tissues from pathogens and harmful moieties, it may also be considered a metabolic barrier, expressing and realizing certain enzymes, as well as a transport platform due to the existent uptake and efflux transporters (Rhea et al. 2019). A physiologically healthy BBB is composed of endothelial cells, which form the walls of the brain capillaries and represent its principal constituent, glial cells – astrocytes, a basement membrane located in-between, and pericytes, supporting the integrity of the vascular structure (Fang et al. 2017). Brain endothelial cells differ from those in peripheral vessels: they exhibit higher mitochondrial and lipid levels and absence of pinocytotic activity or fenestrations in their structure, which restrict the permeability of small molecules (Bors and Erdo 2019). In addition, they are interconnected via protein complexes – tight junctions and adherens junctions, further hindering drug transport across BBB, especially in the case of water-soluble compounds (i.e., paracellular transport) (Kadry et al. 2020). Endothelial cells are set apart from neurons and astrocytes by a basement membrane, which is involved in the formation of blood vessels, signal transduction, and overall support of the vascular structure (Thomsen et al. 2017; Xu et al. 2018). Astrocytes constitute most non-neuronal cells in the brain and participate in the synthesis of apolipoprotein E (apoE) and the maintenance of homeostatic balance via regulation of ion (K+) exchange, neurotransmitters concentration, and nutritional compounds (Gee and Keller 2005; Nagpal et al. 2013). Another essential constituent of the neurovascular unit are pericytes, which are responsible for the angiogenesis, regulation of brain blood flow, and capillaries` diameter and contribute to the immune cell response due to their phagocytic activity (Bors and Erdo 2019). However, in the case of most neurodegenerative diseases and brain neoplasms, significant alterations in BBB's structure and vascularity are observed, either as part of the etiology of the pathologies or as a consequence thereof. In general, BBB's dysfunction manifests as increased permeability, neuroinflammation, and ultimately neuronal damage as a result of interrelated factors such as tight junctions` disruption, higher transcytosis rate, changes in the transporters, the release of inflammatory mediators (cytokines), oxidative stress (Ericson and Banks 2013; Saraiva et al. 2016). Ideally, the changes in the BBB structure should be considered case by case in the drug / drug nanocarrier development process.

Several potential routes have been proposed regarding the transport mechanisms across the BBB, as illustrated in Fig. 1.

Depending on the energy necessity, the transport mechanisms may be broadly classified into passive (transcellular and paracellular diffusion) and active (adsorptive transcytosis, receptor-mediated transcytosis, carrier-mediated transport) (Sánchez-Navarro et al. 2017). Transcellular diffusion (transcytosis) is characteristic of small lipid-soluble compounds (e.g., $CO_2$, ethanol), which passage through

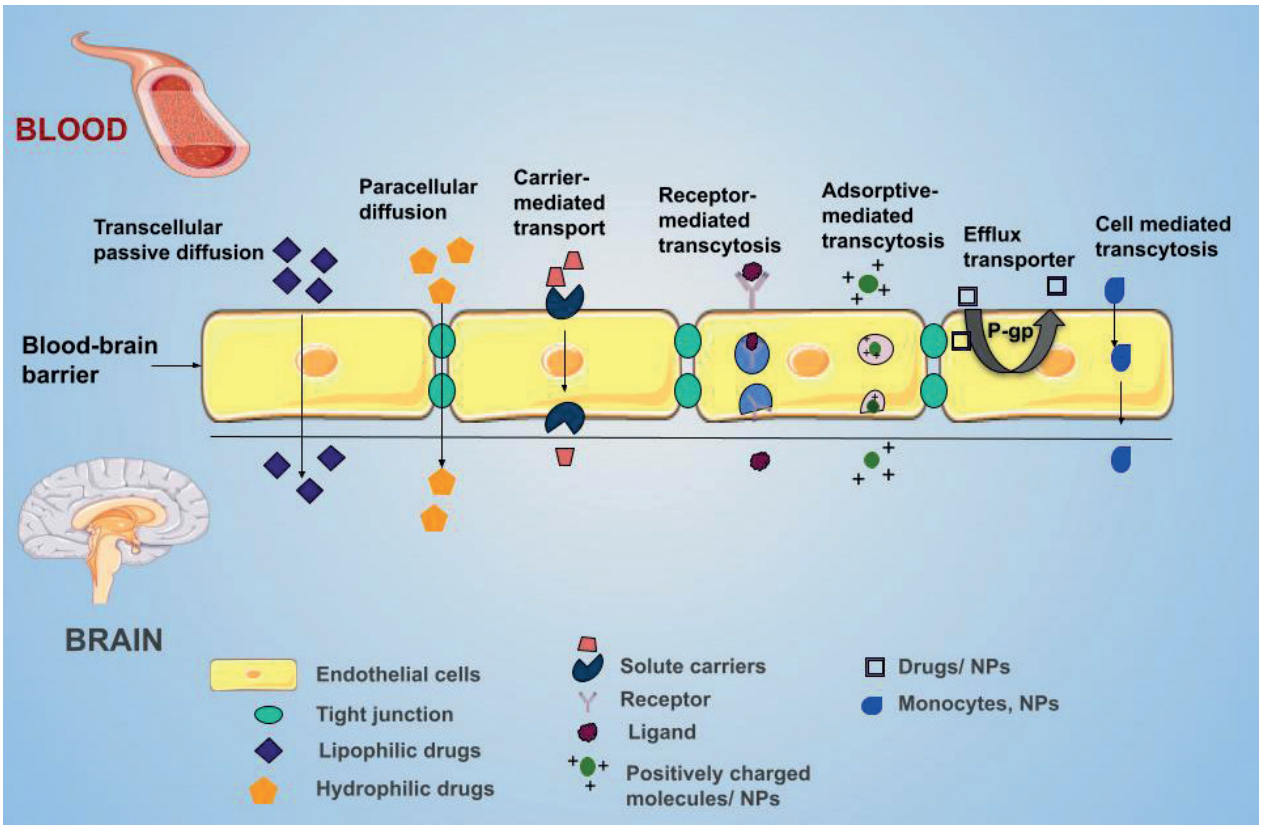


**Figure 1.** Transport mechanisms across the blood-brain barrier.

cells in a non-saturable and non-competitive manner (Dong et al. 2018). This mechanism is highly dependent on drugs` physicochemical characteristics such as ***molecular weight*** (less than 400Da); ***lipophilicity*** – log Po/w between 5–6, or log D value between 0 and 3 (the latter also includes the partition of ionized forms at pH 7.4); ***hydrogen bonds*** (the cumulative number usually < 8), ***polar surface area*** (< 60–70 Å2), ***molecular shape*** (i.e., spherical molecules without branching permeate easily), ***charge*** (positive) (Fong 2015; Kadry et al. 2020). Paracellular diffusion occurs between the endothelial cells due to the negative concentration gradient between the compartments. In addition, the presence of tight junctions limits the permeation of most of the solutes except for small hydrophilic molecules (Mw < 400 Da) (Satapathy et al. 2021).

Active mechanisms transport drugs across the BBB by using different targeting moieties, such as transporters, receptors, etc., or by an unselective approach, as in adsorptive-mediated transcytosis (Sánchez-Navarro et al. 2017). The latter arises from the electrostatic interaction between positively charged drugs/macromolecules/nanoparticles and the negatively charged membrane surface (Hersh et al. 2022).

Receptor-mediated transcytosis is one of the most prospective strategies for drug/nanocarrier delivery across the BBB. It facilitates the selective uptake of various macromolecules (proteins, peptides) by interacting with the receptors expressed on the endothelial cell's membrane (Ahlawat et al. 2020). This transport mechanism may also be implemented in nanoparticle drug delivery by properly conjugating the carriers with specific ligands. Among the most often exploited targets are the receptors for transferrin, insulin, low-density lipoprotein (LDL), lactoferrin, and leptin (Fang et al. 2017). The process involves several aspects: the formation of an endocytotic vesicle, resulting from the interaction between the ligand and the relevant receptor, its internalization into endothelial cells, and subsequent exocytosis into the brain parenchyma (Abbott et al. 2010). However, a possible constraint associated with this mechanism may be noted in the occurring connection between the receptor and carriers` ligand, which in this case, is too strong and may negatively influence the exocytosis process (Tosi et al. 2015).

Brain endogenous transporter systems are involved in CNS delivery via carrier-mediated transport or active efflux transporters. Carrier-mediated transport is implemented by solute carriers (SLC), which assist the bi-directional movement of essential nutrients such as glucose, amino acids, nucleotides, vitamins, etc., mediated by a concentration or electrochemical gradient (Bellettato and Scarpa 2018). Some examples of solute carrier transporter proteins include glucose transporter 1 (GLU 1), large neutral amino acid transporter 1 (LAT 1), monocarboxylic acid transporter 1 (MCT1), concentrative nucleoside transporter 2 (CNT 2) (Tang et al. 2021). To utilize this transport mechanism for drug delivery purposes, the drug's structure needs to be tailored, so it can structurally mimic one of the endogenous substrates or their surfaces (respectively also nanocarriers` surfaces) to be conjugated with suitable substances, transferred via this route (Grabrucker et al. 2016). Active efflux transporters

are responsible for the excretion of various xenobiotics or endogenous substances from the brain to the blood circulation, thereby limiting therapeutic agent accumulation in the CNS (Lombardo et al. 2020). Large hydrophobic molecules containing oxygen or nitrogen atoms are the preferred substrate for efflux transporters. Therefore, increasing drug lipophilicity to improve brain delivery isn't the ultimate successful approach (Bellettato and Scarpa 2018). ATP-binding cassette (ABC) transporters represent a superfamily of efflux proteins, most thoroughly studied of which are: P-glycoprotein (P-gp), Multidrug Resistant-associated Proteins (MRPs), and Breast Cancer Resistance Protein (BCRP) (Catalano et al. 2022).

In addition to the already discussed transport mechanisms, drug delivery to the brain may also be achieved via cell-mediated transport. The immune cells (neutrophils, macrophages, lymphocytes) associated with inflammatory and other pathological conditions are reported to penetrate successfully across the BBB without compromising its integrity (Ding et al. 2020; Ayer et al. 2021). In this regard, drugs or nanocarriers may be tailored to activate immune cell uptake or improve their direct entry into the target area (Tang et al. 2021). This approach was implemented by Ayer et al., which developed T cells-modified polymeric nanoparticles, which can successfully deliver drugs to the brain, as confirmed by *in vitro* and *in vivo* studies (Ayer et al. 2021).

## Lipid-based nanoparticles – factors affecting BBB delivery

The colloidal delivery approach as a brain access strategy has gained enormous attention over the years due to the advantages various nanocarriers provide, such as improved solubility/stability and bioavailability of incorporated active agents, protection from environmental factors (i.e., enzyme degradation), possibility to adjust biodistribution, including target specificity (Santander-Ortega et al. 2017). Among various colloidal systems, SLNs and NLCs are widely exploited for brain delivery purposes due to their biocompatibility and biodegradability profile, intrinsic ability to cross the BBB because of their nano dimensions and lipid nature, as well as the opportunity for production with desired reproducibility (Tapeinos et al. 2017). SLNs are colloidal systems ranging between 50 and 1000 nm composed of solid at room and physiological temperature lipids dispersed in an aqueous medium (Czajkowska-Kośnik et al. 2019; Duan et al. 2020). They can accommodate hydrophobic and hydrophilic compounds, providing controlled and sustained drug release. The most used types of solid lipids include fatty acids, waxes, and mono/di/triglycerides, which may reach up to 30% (w/w) of the composition and are dispersed in an aqueous phase stabilized by surfactants (between 0.5% and 5% (w/w) (Naseri et al. 2015). The relatively limited drug loading space and the predisposition for drug expulsion during storage, may outline certain limitations of SLNs, both successfully overcome by NLCs (Mishra et al. 2018). Often referred to as second-generation SLNs, NLCs are composed of a mixture of solid and liquid lipids arranged into less ordered (compared to SLNs) structures, characterized by voids and accessible areas, hence enhanced capacity for drug loading. In addition, they exhibit improved physical and storage stability (Müller et al. 2016; Czajkowska-Kośnik et al. 2019). The liquid lipid fraction (generally between 0.1% and 30% of the total lipid mixture), represented by mineral or vegetable oils, should be carefully selected concerning its physiological tolerability, solubility properties, and solid lipids compatibility (Elmowafy and Al-Sanea 2021). The solid/ liquid lipid ratio and the total lipid phase concentration highly affect the physical stability of NLCs, as reported by Loo et al. According to the authors, NLCs with the highest lipid concentration (30% w/w), highest solid/liquid lipid ratio (90:10) and further inclusion of propylene glycol exhibit superior physical stability in comparison to lower total and solid lipid concentrations (Loo et al. 2013). The physicochemical parameters of elaborated nanocarriers, such as size, shape, zeta potential, and surface modification, are other vital factors to be considered and respectively tailored during the formulation process since they highly influence the mechanisms of uptake across BBB, drugs release kinetics and target specificity (in case of ligand conjugation).

### Size

The size of the NPs is a crucial physicochemical parameter, affecting their biodistribution, transport across biological membranes, targeting properties, and clearance from the body (Satapathy et al. 2020). Furthermore, particle size and size distribution patterns also significantly impact NPs` characteristics, such as entrapment efficiency, physical stability, and drug release kinetics (Seko et at. 2020). The "ideal" NPs size range for brain delivery is still a scientific subject. A diameter of 10 nm is often reported as the lowest limit for the NPs to withstand renal excretion, whereas, for the upper limit, some reports indicate diameters up to 100 nm and others up to 300 nm (Sousa et al. 2019; Pinheiro et al. 2021; Hersch et al. 2022). According to Pinheiro et al. most nanocarriers intended for brain delivery purposes are within the range of 100–300 nm (Pinheiro et al. 2021). Nanoparticle size directly impacts their uptake mechanism – carriers up to 200 nm are taken up by clathrin-mediated endocytosis, whereas larges NPs (up to 500 nm) by caveolae-mediated (Wohlfart et al. 2012). Sadegh Malvajert et al. elaborated on curcumin-loaded SLNs/ NLCs and evaluated in a comparative aspect their brain accumulation. According to the authors, the NLCs increased brain absorption of curcumin (4-fold compared to SLNs). In addition, they exhibited superior CNS retention, which may be due to their smaller size (117 nm vs. 204 nm), as well as due to Tween 80 present at their surface, which is known to inhibit the efflux protein P-glycoprotein and thereby hinder drug efflux from CNS (Sadegh Malvajert et al. 2018).

## Shape

The shape of NPs is also known to affect their cellular uptake (Saraiva et al. 2016). In contrast to inorganic nanoparticles, which may have different shapes, including spherical, rod-like, cubic, etc., lipid nanoparticles are usually sphere-like, although some irregularly shaped NLCs were also reported in the literature (Jia et al. 2010; Wang et al. 2019). In their study, Jia et al. developed silybin-loaded NLCs, evaluating the effect of liquid lipid fraction on the physicochemical characteristics of the NPs and, according to the authors, increasing liquid lipids up to 30% lead to the formation of irregularly shaped NLCs, exhibiting the highest entrapment efficiency values (Jia et al. 2010). However, most often, the NPs intended for brain delivery exhibit a spherical shape, allowing easier reproducibility and subsequent surface modification (Ding et al. 2020).

## Charge

Surface charge is another physicochemical characteristic affecting the transport of NPs across the BBB and their internalization. In general, cationic nanoparticles are hypothesized to be more easily internalized than their anionic or neutral counterparts due to the electrostatic interaction with the negatively charged proteoglycan (Honary and Zahir 2013). In their study, Gabal et al. elaborated small (< 200 nm) anionic and cationic NLCs and investigated the influence of surface charge on their brain delivery by intranasal administration. As reported by the authors, the cationic NLCs exhibited higher maximum concentration (Cmax) and absolute bioavailability compared to the anionic NLCs. However, the conducted toxicity studies revealed also their lower tolerability manifesting in severe inflammation (Gabal et al. 2014).

## Surface properties

Surface modification of the drug carriers is a widely exploited approach in nanotechnology to improve drug performance and therapy outcomes. A well-known strategy is coating nanoparticles` surfaces with hydrophilic polymers such as polyethylene glycol (PEG) to minimize recognition by the reticuloendothelial system and provide prolonged circulation time (Rizwanullah et al. 2016). Furthermore, its

**Table 1.** Recent SLNs and NLCs formulations for brain delivery (201-022).

| Type of nanocarrier | Composition | Surface modification | Target * moiety | Drug | Obtained results | Reference |
|---|---|---|---|---|---|---|
| SLNs | Cetyl palmitate, Tween-80 | β-hydroxybutyric acid-stearyl amine conjugate | MCT-1 receptor | Carmustine temozolomide | Improved brain uptake; enhanced antitumor activity vs. free drugs | Ak et al. 2021 |
| SLNs | Sodium behenate, polyvinyl alcohol 9000/12000 | Transferrin, insulin, ST-MBS /ST-PEG-MBS linker | TfR; IR | Dodecyl-methotrexate | PEGylated functionalized SLNs successfully overcame BBB | Muntoni et al. 2019 |
| SLNs; NLCs | Cetyl palmitate, Tween 60, Cetyl palmitate, Tween 60, Miglyol-812 | Transferrin, (conjugated to DSPE-PEG(2000)-$NH_2$) | TfR | Curcumin | Improved curcumin permeation (1.5-fold) through BBB according to permeability study on hCMEC/D3 cells | Neves et al. 2021 |
| SLNs; NLCs | Cetyl palmitate, Tween 80 Cetyl palmitate, Miglyol-812, Tween 80 | RVG29 peptide (conjugated to DSPE-PEG2000-MAL) | nAChR | Quercetin | High quercetin EE% (>80%); improved permeability through BBB vs. non-functionalized NPs, neuroprotective properties | Pinheiro et al. 2020 |
| SLNs | Dynasan 116 | ApoE | LDLR | Donepezil | Improved brain uptake vs. plain NPs | Topal et al. 2021 |
| | Tween 80 | DSPE-PEG-avidin | LRPs | | 2-fold higher penetration of ApoE-SLNs in a BBB model vs. plain SLNs | |
| NLCs | Compritol 888 ATO, MCT 812, Myrj 52, soy lecithin, mPEG-MAL, mPEG-OH | Monoclonal antibody OX26 | TfR | Salvianolic acid B, Baicalin | Improved drugs uptake by RME; enhanced bioavailability | Wu et al. 2019 |
| NLCs | Palmityl palmitate | Lactoferrin (Lf) | LDL | Nimodipine | Successful intracellular delivery in stroke cell model via LF-RME | Zhao et al. 2018 |
| | Miglyol 812 | DSPE-PEG2000-COOH | | | | |
| | SPC, Solutol HS15 | | | | | |
| SLNs | Glyceril monostearate, stearic acid, soya lecithin, Tween 80 | Angiopep-2 | LRP 1 | Docetaxel | Improved cellular internalization and cytotoxicity; prolonged circulation vs. free drug | Kadari et al. 2018 |
| SLNs | Triasterin, HSPC, DSPE, cholesterol | Tween 80-coating | P-gp; FRs | Folic acid-doxorubicin conjugate | The conjugated SLNs were successfully internalized in U87 MG brain cancer cells; high antitumor activity | Jain et al. 2022 |
| NLCs | Stearylamine, Precirol ATO5, Capryol PGMC, Tween 80, Poloxamer 188 | Transferrin | Tf-receptor | Rapamycin | High EE%, small size; high cellular uptake vs. plain NLCs; no immunosuppressive effect | Khonsari et al. 2022 |

*Legend: ApoE- Apolipoprotein E; DSPE-PEG-NH2 – 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000] (ammonium salt); DSPE-PEG2000-MAL- 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(polyethylene glycol)-2000] (ammonium salt); EE –entrapment efficiency; FRs- Folate receptors; hCMEC/D3- human cerebral microvascular endothelial cells; HSPC- hydrogenated soybean phosphatidylcholine; IR- insulin receptor; LDLR- low-density lipoprotein receptor; LRPs- low density lipoprotein receptor-related protein; MCT-1 receptor- monocarboxylate transporter-1; MCT 812- Medium Chain Triacylglycerol 812; mPEG-MAL- Methoxy polyethylene glycol maleimide; mPEG-OH- Methoxypolyethylene glycol; nAChR- nicotinic acetylcholine, receptors; RME- receptor mediated endocytosis; SPC- sphingosylphosphorylcholine; ST-MBS –stearylamine 3-maleimidobenzoic acid N-hydroxysuccinimide ester; Tf-receptor- transferrin receptor.

hydrophilic properties lead to forming a protective shield over NPs` surface, advancing their steric stabilization (Suk et al. 2016). The PEGylation approach was adopted by Arduno et al. developing polyethylene glycol stabilized SLNs loaded with platinum (IV) prodrugs as a drug delivery system for glioblastoma multiforme treatment. The *in vitro* studies revealed that the PEGylated SLNs successfully permeated the BBB and exhibited enhanced cellular uptake compared to free drugs (Arduino et al. 2020a). Besides PEG, other hydrophilic molecules, such as Polysorbates, may also be used as surface coating materials, acting oppositely. Polyethylene glycol is known to minimize NPs` opsonization. Polysorbate (Tween) 80 is reported to absorb apolipoprotein E from the blood onto the NP's surface, thereby enabling their transport across the BBB via endocytosis (Cagliani et al. 2019). In their study, Yadav et al. developed Tween 80-coated temozolomide-SLNs, characterized by improved brain uptake and bioavailability compared to plain SLNs and free drugs (Yadav et al. 2018). However, in brain delivery, the NPs` active targeting via surface modification is of most interest. The functionalization with specific ligands/ monoclonal antibodies, selectively interacting with the corresponding BBB's receptors, provides the possibility to internalize the drug-loaded carriers via physiological mechanisms (e.g., receptor-mediated transcytosis, carrier-mediated transport) (Pinheiro et al. 2021). An interesting approach was adopted by Arduino et al., which elaborated transferrin functionalized MC111-loaded NLCs aiming to promote P-glycoprotein and BCRP transporters expression. The decreased level of both transporters is part of Alzheimer's disease pathology; therefore MC 111 was selected as a specific ligand to enhance both transporters' activity. The subsequent functionalization of the nanocarriers with transferrin provides the possibility to explicitly target the brain endothelial cells and activate the expression of both transporters (Arduino et al. 2020b). A summary of recently developed brain targeting SLNs and NLCs is provided in Table 1.

## Conclusion

The numerous pathologies of CNS and the physiological constraints of the blood-brain barrier determine the constant progress of nanotechnology in this application area. Due to their composition compatibilities, excellent tolerability profile, and scaling-up capabilities, solid lipid nanoparticles and nanostructured lipid carriers are ideal candidates for brain drug delivery systems. Their subsequent functionalization with targeting moieties facilitates their brain uptake and leads to enhanced cellular internalization in a non-disruptive, physiological manner and improved therapeutic effect.

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