

# Solid Lipid Nanoparticles: A Nano Drug Carrying System in Treatment of Nervous Diseases

Yue Yin <sup>1, †</sup>, Jingyuan Zhang <sup>2, \*, †</sup>, Xinyue Zhou <sup>3, †</sup>

<sup>1</sup> Ulink College of Shanghai, Shanghai, 201615, China

<sup>2</sup> Faculty of Science, Department of Chemistry, University of Alberta, Edmonton, T6G2R3, Canada

<sup>3</sup> Chemical engineering faculty, Monash University, Melbourne, Victoria, 5342, Australia

\* Corresponding author: jz13@ualberta.ca

†These authors contributed equally to this work.

**Abstract.** Solid lipid nanoparticle (SLN) is a unique colloidal system used to deliver drugs which is nontoxic, biodegradable, showing good biocompatibility, and have small particle size. The possibility of SLN to deliver the brain drugs without damaging the brain-blood barrier (BBB) makes SLN an advanced central nervous system (CNS) drug delivery system. SLNs delivering drugs to CNS are mostly prepared by applying high energy homogenization method to achieve a better surface modification. The central topic of this article is how the SLN can overcome the BBB and help treat the central neural system disease. Also, SLNs contain levodopa can go through the BBB to help treat Parkinson's and SLNs coated with chitosan and loaded with ferric acid to treat Alzheimer's Disease (AD) are highlighted in this article. The effectiveness of SLNs compared with traditional therapy is shown in the article. Additionally, further studies are needed to focus on higher encapsulation efficiency and drug load efficiency as well as the targeted intranasal drug delivery.

**Keywords:** Solid Lipid Nanoparticles, Blood-Brain Barrier, Alzheimer's Disease, Parkinson's Disease.

## 1. Introduction

Neurological disorders, also known as the central nervous system (CNS) diseases, are affecting many people's lives over the world, leading to considerable morbidity and mortality [1]. These neurological diseases include brain cancers/tumors, neuromuscular diseases, neurodegeneration, epilepsy, multiple sclerosis (MS), Huntington, Parkinson and Alzheimer's disease. CNS diseases are commonly considered as a result of neuronal death caused by an imbalance of neurological functions. The mechanisms of this imbalance are varying: accumulation of misfolded proteins, lack of production of neurotrophic components, dysfunction of mitochondrial, depletion of activity of endogenous antioxidant enzymes, and occasional defects of genes and molecules. Different causes of CNS disorders present that finding a specific therapeutic treatment for CNS diseases is very challenging. Another obstacle to treating these diseases is the blood-brain barrier (BBB), as it obstructs channels for potential drugs passing through [2], and the efficacy of pharmacokinetics explored by current drugs is inhibited in the brain diseases treatment. Therefore, BBB are required to be explored detailly when developing drugs and drug delivery systems for more efficient cure strategies for CNS diseases.

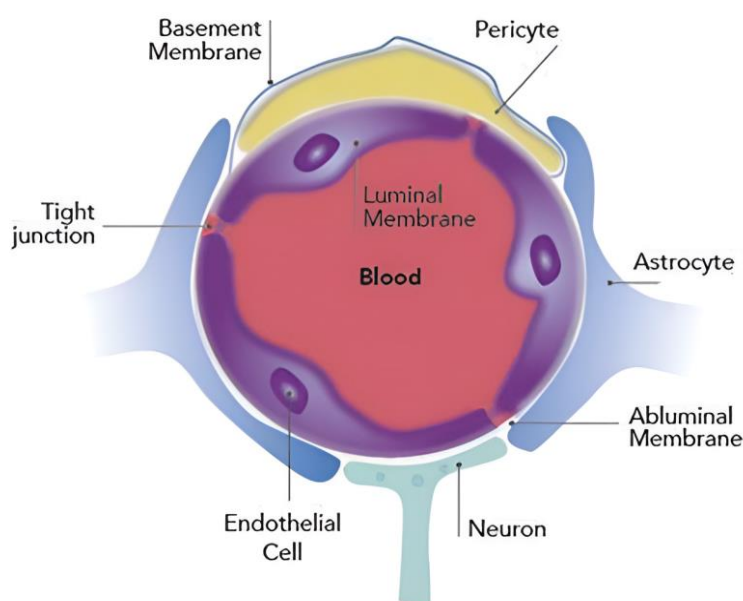
Nowadays, rapid advances in nanotechnology and nanoparticle production have been revolutionizing the pharmaceutical industry. As properties of nanoparticles change with particle sizes, nanoparticles provide opportunities for developing new therapeutic approaches [3]. Solid lipid nanoparticles (SLNs) with particle size between 40 to 1000 nanometers and made of solid lipids such as triglycerides, cholesterol, and stearic acid [4]. SLNs is one type of nanocarriers which are safe and inexpensive and can cross BBB to carry drugs to desired brain sites using an effective, less toxic and secure manner. Due to biocompatibility and chemical versatility of lipid nanoparticles, SLN can generate many benefits to be used as drug delivery system, thus, it can be an alternative to emulsions, polymeric nanoparticles and liposomes [5]. Fundamentally, its kinetic stability is excellent and its

morphology is rigid, meaning that it is a good candidate to protect drug or active ingredients from body environment and release them properly. In addition, comparing with traditional nanocarriers, primary advantages of SLNs include higher loading capacity, decreased toxicity [6], possibility of production at industrial scales and biodegradability [7], reduced solvent usage in preparation stage, modulation of drug release.

Using the brain drug delivery to alleviate various CNS diseases safely and efficiently can be treated as a concerned and continuously progressive topic in pharmaceutical fields. New knowledge and technology are developing rapidly. Even though some previous efforts have devoted to SLNs' properties for CNS drug delivery, drug incorporation models, production methods and applications, they need to be supplemented. In this review, firstly, the functions of BBBs are investigated. Also, the novel synthesizing procedures involving used materials, preparation methods, characterizations and structures affecting applications for SLNs are evaluated in detail. Then, the incorporation model of active drugs into SLNs is explained. Finally, the applications of drug delivery systems composed of solid lipid particles in the treatment of nervous system related diseases have been discussed.

## 2. Blood-brain barrier

The BBB is an important part of the body's neurovascular unit that communicates with the CNS. At the same time, the free flow of chemicals between brain cells and the outside world is limited [8]. The main components of BBB are endothelial cells, astrocytes, basement membrane, tight junctions and pericytes, which are shown in Figure 1. The key structure of the BBB, which provides the barrier, is the endothelial tight junction. Endothelial cells in the capillaries that make up the BBB are so close together that they create tight junctions. Because of the tight space, only small fat-soluble chemicals and certain gases may get through the capillary wall and into the brain tissue. Larger molecules, such as glucose, can enter via transporters rather than passing through the BBB directly. Other BBB components surround blood artery endothelial cells, which are not strictly involved in blocking objects from reaching the brain, but instead connect with the cells that compose the barrier to vary the BBB's selectivity.



**Figure 1.** Cross-section of a microvessel in the BBB [9].

Various strategies have been developed to deliver active therapeutic agents to the brain to treat neurological diseases. In general, drugs can be injected into the brain, or delivered directly to the brain through a catheter or after invasive surgery. In this drug delivery strategy, drug loaded polymer biodegradable materials can be implanted into specific parts of the brain to achieve sustained drug release. Local route of administration is one of the most invasive routes of administration. Although

it is exceedingly successful in animals, over 90% of small molecule medications and almost 100% of big therapeutic pharmaceuticals cannot cross through the BBB when treating actual human patients [10]. Furthermore, efflux transporters such as P-glycoprotein 1 [11] may actively transport a few medicines that may cross the BBB back to blood vessels. Drug resistance can be caused by active efflux transporters that identify a wide range of substances. Therefore, it is necessary to have stable pharmacological effects and less trauma in the way of administration. The nasal route of delivery is also intriguing, as it allows medicines to circumvent the BBB and enter the brain directly [12]. After reaching the nasal cavity, active drugs are loaded in some nano carrier systems and reach the brain through olfactory pathway and trigeminal pathway [13]. Nevertheless, due to the inconsistent release dose of the target, the intranasal pathway is not an ideal method. So far, systemic drug administration has been the most thoroughly researched and widely accepted method of delivering medications to the brain. However, the main obstacle to this drug delivery strategy is BBB. A way must be created to load active drugs into non-toxic, permeable nanoparticles that can cross the BBB. In any case, the destruction of BBB will lead to the inevitable influx of neurotoxins, causing serious damage to the brain. As a result, sophisticated drug modification tactics may aid in improving medications' capacity to penetrate the BBB, so as to treat nervous system diseases and avoid neuronal dysfunction caused by the destruction of BBB. Lipid nanoparticles can pass through BBB safely and effectively, showing exciting drug delivery effectiveness in applications [14].

### 3. Preparation and characterization

#### 3.1. Starting material for preparing SLNs

There are several structures of SLNs. In general, there are two kinds of SLNs: they are SLNs with a solid core and nanoemulsions with a solid shell. Solid lipid, surfactant, water and liquid lipid (if the core of the particle is liquid ingredient) is needed during the preparation of SLNs. The structure of SLN have several effects on its drug release behavior. Also, the lipid concentration, ratio of the emulsifier lipid, time of homogenization will lead SLNs to show different properties [15]. Although to build a SLN which have desired characteristics needs starting materials that have good properties, it should be took into consideration of the cytotoxicity of the starting material to guarantee the bioavailability.

Lipid is important in the structure of SLNs. It is used to mix the active compound and form the inner matrix of the solid lipid core. The lipid selected to prepare SLNs will have an effect on the properties (including their size, appearance, stability and cloud point) of the final obtained colloidal [16]. Fatty alcohols, glycerol esters, free fatty acid and wax are the common starting lipid material of the SLNs.

During the preparation of the SLNs, stabilization stabilizes the inner lipid core and stops the core from degradation. Mostly, when preparing SLNs, surfactants are used as the stabilization reagent of the SLNs between the lipid prepared for SLNs and the water. According to the properties of the surfactant, it tends to accumulate around the lipid and form a product in the morph of a particle. There are different types of surfactant including the non-ionic surfactant like sorbitan monolaurate, anionic surfactant like sodium glycolate, cationic surfactant, amphoteric surfactant and the co- surfactant. Surfactants determined to prepare the SLNs will give the particle different stability properties [17].

#### 3.2. Preparation of SLNs

Many methods are used in the preparation of SLNs, most of the synthesis of the SLN need to go through the homogenization process to obtain a mixture containing active compound, lipid, surfactant, and water, then separate the mixture to the particles in the nanoscale [18].

There are two different ways to prepare the homogenization intermediate. The first one is the homogenization process which needs to consume higher energy. This kind of process always needs to heat the mixed intermediate up to a certain high temperature. When applying this homogenization method, the surface of the SLNs prepared will become easier to be modified. One reported method

using this homogenization method is the ultra-sonication technique. In this method, SLNs are directly prepared in the lipolysis buffer. Raw materials are mixed and heated in the buffer to form a microemulsion and the homogenization process is conducted by applying the ultrasonication probe directly into the mixture [19].

Another process is the homogenization method requires lower energy. In this kind of process, less energy is required to form a homogeneous phase. PIT (phase inversion temperature) method is one reported method of such processes. In this method, SLNs are prepared in the aqueous solutions mixed with lipid where the ratio of lipid and aqueous solution is an exact value. Then the mixture is heated to the phase inversion temperature to form the homogeneous intermediate of the SLNs [20].

### 3.3. Characterization of SLNs

The characteristics of SLNs including the size, morphology and the electrokinetic behaviors. SLNs' characteristics are controlled by the starting material, the preparation method and will be affected by the contamination during the preparation and the storage method and storage time. To determine if the SLN possesses the desired properties, several characterizations are needed to analyze the SLNs.

The size of the SLNs can be analyzed by the Laser Diffraction (LD), and Dynamic Light Scattering (DLS), it is reported that DLS is the most frequently used technique to analyze the size of SLN. As most of the SLNs are separated in the colloidal solution, zeta-potential can determine the condition of such kind of solution [19].

When SLNs are applied in the pharmaceutical industry, drug load capacity is also necessary to be determined. This parameter expresses the efficiency of the SLNs in transporting a certain kind of drug. The SLNs' drug load capacity is determined by the surfactants properties, lipid and the particle structure. Drug load capacity shows the ratio of the drug and the total particle weight. Another parameter called encapsulation efficiency expresses the ratio between the drugs entrapped in SLNs and the drugs that separated in the intermediate mixture during the preparation. The drug load efficiency shows how many drugs will an SLN particle contain and the encapsulation efficiency will indicate that to prepare a unit amount of SLNs that contains one kind of drug, how many starting materials are needed during the preparation process [16].

Also, when studying how the drugs interact with SLNs and if the drug will react with the lipid chosen to build particles, Fourier Transform Infrared Spectroscopy (FTIR) is a good method to determine the composition of the SLNs by studying the chemical bond contained in the particles [21].

## 4. Different models for drugs incorporation in SLNs

### 4.1. Model constructed homogeneously

In the lipid matrix model constructed homogeneously, drugs can either form uncrystallised clusters or can be randomly distributed in the lipid matrix randomly. This homogeneous matrix can be obtained by a homogenization method at a low temperature with low-to-non-lipophilic drugs and a homogenization method at a high temperature with quiet lipophilic drugs. During the low-temperature homogenization process, the dispersed and dissolved drugs will be encapsulated by bulk lipid nanoparticles and high-pressure conditions will exert great mechanical forces to break these encapsulations into small forms with homogeneous sizes. During the high-temperature homogenization process, the solid lipid particles attached to drugs. They are firstly heated from oily droplets and then cooled. During the cooling stage, no crystallization and phase separation between drugs and lipids are detected, and hence a homogeneous matrix is obtained. This type of model is found to be valid for incorporating prednisolone drugs and the release speed of this drug-mediation by a homogeneous lipid matrix is approximately 1 day to several weeks.

### 4.2. Model with enriched drugs on the shell structure

In this model, the core area of the lipid nanoparticles is empty of drugs. On the contrary, the shell region is filled and loaded with drugs owing to a phase separation that happened in the cooling

procedures. The drug compounds-enriched shell model is prepared by a high-temperature homogenization approach. When obtained liquidus oil drops loaded with drugs reach recrystallization temperature, the lipid parts recrystallize toward the center core direction, simultaneously leaving back the parts of liquid drugs in the shell region. One drawback of this type of drug incorporated SLNs is the quicker burst release of drugs compared with the homogeneous model, because all drugs deposit at the large-surface outer layer. Some strategies can be adopted for controlling this undesired burst release and elongating the drug release period: (1) substituting small lipophilic drugs with larger ones such as micro-sized drugs; (2) replacing high concentration surfactants with lower concentration ones.

#### 4.3. Model with enriched drugs on the center region

In this model, almost all the drugs are concentrated in the core area and the outer shell is composed of SLNs. The reason is that the precipitation of drugs toward the core center is earlier than the crystallization of solid lipid particles. The drug release profile for this SLNs model is controlled by the intrinsic properties of the solid lipid membrane and complies with Fick's diffusion law. [22].

## 5. Applications of SLNs in CNS diseases treatment

### 5.1. SLNs for delivering drugs for Alzheimer disease

As BBB is a main obstacle for allowing drugs to take effects on brain disorders, SLNs are considered promising biomedical tools to overcome this obstacle for drug delivery [23].

Drug-loaded SLNs have been demonstrated to be more suitable for brain drug delivery as they have higher accumulation in the brain and have targeted delivery potentials for the brain [24]. The SLN with active drugs can arrive at abnormal spots in the brain via inhalation, oral dosage, and parenteral pathways to interfere with the signaling channels of malfunctioned nerve cells; thus, neuro pathologies symptoms could be alleviated [25].

Alzheimer disease (AD) is defined as an accumulatively neuro degenerative disorder which often happens on the elderly people. The reason is that the dysfunction of cholinergic neurons, causing frequent loss of cognitive functions, dementia, change of behaviours and fatal risks [26]. Existing therapeutic treatment mainly based on the development of cholinesterase inhibitors for cholinergic malfunction. Drugs that can behave as cholinesterase inhibitors and confirmed by Pure Food and Drug Administration are rivastigmine, donepezil, and galantamine. Their pharmacological effects are all restricted by a low concentration of drugs on the site of the brain resulting from the blood brain barriers. SLNs developed as nano-drug delivery approaches can help to improve the brain tissue accessibility of these active biomolecules and their efficacy of therapy [27].

For recent research findings, Sumant et.al. designed a SLN coated with chitosan and loaded with ferulic acid for effective treatment of AD through central composition design between the lipid and surfactant. The utilized lipid is Compritol and surfactant is polysorbate 80. Characterisation techniques (FTIR, DSC, PXRD, FESM) demonstrate that compatibility of ferulic acid in the formulation, drug crystallinity loss, spherical nanoparticle form with less agglomeration. Through preclinical tests in vivo and in vitro in goat mucosa and rats, this ferulic acid loaded SLN is showed to have a promise for AD treatment through intranasal pathways, improving the cognitive capability through reduce latency time, drug obtainable amount by body, intranasal cell permeation and adhesion, drug release efficiency, anti-Alzheimer diseases efficacy, safety, and potency. *Salvia officinalis* is another substance which has the ability to prevent and treat AD. Elena et al. adopted this bioactive substance and integrated it with the secondary generation of SLNs called nanostructured lipid carriers (NLC) to develop *salvia officinalis* freeze-dried extractions loaded NLC for AD treatment [28]. Results show that loaded NLC has higher loading capacity for drugs, brain targeting characteristics, elongated and stable drug release, higher protein adsorption, and superior antioxidative functions compared with stand-alone *salvia officinalis*. Gizem et al. developed a lipid nanoparticle labeled with rhodamine-B to transfer the donepezil drug efficiently to treat Alzheimer's disease. This drug delivery nano system is targeted to a ligand called apolipoprotein combining BBB

receptors, resulting in an increase of SLNs uptake by neurons and endothelial cells in the brain and an enhancement of drug delivery through brain endothelial cells with desired drug release profiles. Galantamine loaded SLN is the most efficient AD drug, which is prepared by Tween 80 surfactant using emulsification–diffusion approach, exhibiting uniform distributed particle size(752~792nm) and polydispersity (0.432), and the desired Z-potential (11.8~17.8 mV) [29].

### 5.2. SLNs for delivering drugs for Parkinson disease

The disease of Parkinson (PD) is also categorized as the neurodegenerative disease like AD. SLNs can encapsulate levodopa by micro-emulsification method to overcome the limited ability of levodopa crossing the BBB and improve the efficacy to treat Parkinson's disease. Ropinirole (RP) is a novel developed dopamine agonist drug applied for PD mitigation via oral dosage. The limitations of this drug are low bioavailability in the oral environment and high dosing frequency needed [30]. Therefore, to improve the applicability of ropinirole in alleviating syndromes of PD, the effort to increase its pharmacokinetics and pharmacodynamics is required. Considering the advantages of using SLNs, Narendar et al. designed, optimized and evaluated ropinirole loaded SLNs [31], and hydrogel containing ropinirole loaded SLNs formulations, finding that RP-loaded SLNs and RP-loaded SLNs hydrogels have better permeations and drug release stability compared with conventional formulations. For the pharmacokinetics evaluation, the enhancement factor of hydrogel containing SLNs is 3.0 which is better than that of hydrogel-free SLNs with a factor of 2.1. For the pharmacodynamic evaluation, this type of loaded SLNs in a hydrogel formulation can uptake more drugs including glutathione and dopamine, and the levels of unwanted catalase and peroxidation of lipid are reduced. Similarly, anti-Parkinson's disease drug named piribedil can also be incorporated into a SLNs gelling system to rise the bioavailability of the drug and decrease the dosage frequency, which has been demonstrated by Chandra et al. via pharmacokinetic and pharmacodynamic investigations. Stefania et al. reported a novel SLNs prepared by glycol chitosan with dopamine loaded have larger drug encapsulation capacity with smaller size of particles compared with dopamine loaded SLNs which are not prepared by glycol chitosan [32]. Besides, SLNs incorporated with dopamine are proved to be stable thermally. This novel SLN formulation with potential better properties opens a window for future improvement direction for the SLNs used in Parkinson's disease therapy.

### 5.3. SLNs for delivering drugs for epilepsy

Epilepsy is a long-term disorder in which neurons in the brain activate improperly, causing transient brain impairment. The goal of pharmacological treatment for epilepsy is to reduce seizure frequency and severity while limiting brain and other tissue damage [33].

In this case, the therapies' limitations include insufficient drug concentration at the target region of the brain due to the BBB acting as a barrier. A nano-technological SLN-based strategy has shown potential gains in overcoming current constraints in the treatment of epilepsy among the traditional and newly discovered drug delivery systems [34].

### 5.4. SLNs for delivering drugs for ischemic stroke

Ischemic stroke refers to the death of brain tissue due to narrowing or occlusion of the arteries supplying blood to the brain and insufficient blood supply to the brain. Transient ischemia attack, reversible neurological impairment, progressive stroke, and complete stroke are all examples of ischemic strokes.

The primary therapeutic strategy should focus on reducing proinflammatory effects and providing neuroprotection. Due to the limited absorption of medicines across the BBB, conventional therapeutic techniques are ineffective. A new therapeutic technique based on enhanced nano drug delivery might help overcome key obstacles in drug targeting for stroke therapy. One of the current nanotechnological techniques looking at prospective medication formulations for ischemic stroke therapies is SLN carrier-based drug delivery [35].

### 5.5. SLNs for delivering drugs for other neurodegenerative disease

Oxidative stress is a condition in which the body's oxidation and antioxidant actions are out of balance, resulting in neutrophil infiltration, increased protease release, and the generation of a significant number of oxidative intermediates. According to one research, SLNs encapsulating LA can be employed for topical LA distribution as an anti-aging drug, with improved stability and hydrophilicity. LA-MEM loaded SLNs showed no cytotoxicity and could publish the free codrug in vitro stability and release experiments in both simulated gastric and simulated intestinal fluid, as well as early in vitro cytotoxicity testing [37].

## 6. Conclusions

After the critical analyzing in this review, the lipid based and non-toxic SLN have small particle size showed an advantageous performance in delivering drugs across the brain blood barrier (BBB) without causing any damage on the BBB. This advantage makes SLN an excellent alternate for polymer nanoparticles and liposomes in treating CNS disease which needs to deliver drugs directly to the brain system.

The SLN have different matrix models due to the phase separation during the preparation. And those difference in models contribute to the control of drug release rate. They are the homogeneous matrix model have the drug release period of one day to several weeks, drug compounds-enriched shell model lead to a shorter drug release rate and drug compounds-enriched core model whose drug release rate is caused by the solid lipid membrane choose to coat the core.

In this review, the application of SLN in treating CNS diseases are mainly focusing on the treatment of AS and PD. For treating Alzheimer's disease, SLN of ferulic acid-coated by the chitosan are developed to improve the bioavailability of the traditional drugs to improve the efficiency of the therapy. Also, for another substance that used to treat AD, SLN is reported to help improve the drug load efficiency and elongate and stabilize the drug release rate. During the treatment of PD, SLNs containing levodopa was reported to show a better efficacy compared with the traditional drugs with the same active compound.

## References

- [1] Choonara E. Yahya, Pillay Viness, Lisa du Toit, et al. Trends in the molecular pathogenesis and clinical therapeutics of common neurodegenerative disorders [J]. *International Journal of Molecular Science*, 2009, 10 (6): 2510 - 2557.
- [2] Patel Medha, Souto B Eliana, Singh K Kamalinder. Advances in brain drug targeting and delivery: limitations and challenges of solid lipid nanoparticles [J]. *Expert Opinion on Drug Delivery*, 2013, 10 (7): 889 - 905.
- [3] Scheffel U, Rhodes BA, Natarajan Tharini, et al., Albumin microsphere for study of the reticuloendothelial system [J]. *Journal of Nuclear Medicine*, 1972, 13 (7): 498 - 503.
- [4] Sjöström Brita, Kronberg Bengt, Carlfors Johan, A method for the preparation of submicron particles of sparingly water-soluble drugs by precipitation in oil-in-water emulsions. I: influence of emulsification and surfactant concentration [J]. *Journal of Pharmaceutical Science*, 1993, 82 (6): 579 - 583.
- [5] Kovacevic A., Savic S., Vuleta G., et al. Polyhydroxy surfactant for the formulation of lipid nanoparticles (SLN and NLC): effect on size, physical stability and particle matrix structure [J]. *International Journal of Pharmaceutics*, 2011, 406 (1-2): 163 - 172.
- [6] Pardeike Jana, Hommoss Aiman, Müller H. Rainer, Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products [J]. *International Journal of Pharmaceutics*, 2009, 366 (1-2): p.178 - 184.
- [7] A. Del Pozo-Rodríguez, Delgado Diego, Gascon R Alicia et al., Lipid nanoparticles as drug/gene delivery systems to the retina [J], *J Ocul Pharmacol Ther*, 2013, 29 (2): 173 - 188.
- [8] Bechmann I., Galea I., Perry V.H., What is the blood-brain barrier(not)? [J]. *Trends in Immunology*, 2007, 28 (1): 5 - 11.

- [9] Patel, Goyal Bhoomika, Bhadada Shraddha, et al., Getting into the brain [J]. *CNS Drugs*, 2009, 23: 35 - 58.
- [10] SH. David, Wadajkar S Aniket, Robert Nathan et al., Evolving drug delivery strategies to overcome the blood brain barrier [J]. *Current Pharmaceutical Design*, 2016, 22 (9): 1177 - 1193.
- [11] Gooijer D., Yetkin-Aril B., Tellingen van O., et al., Overcoming the blood-brain tumor barrier for effective glioblastoma treatment [J]. *Drug resistance updates: reviews and commentaries*, 2015, 19: 1 - 12.
- [12] Erdő, Bors A. Luca, Farkas Daniel, et al., Evaluation of intranasal delivery route of drug administration for brain targeting [J]. *Brain Research Bulletin*, 2018, 143: 155 - 170.
- [13] Satapathy Mantosh, Yen Ting-Lin, Jan Jing-Shiun, et al., Solid lipid nanoparticles (SLNs): an advanced drug delivery system targeting brain through BBB [J]. *Pharmaceutics*, 2021, 13: 1183.
- [14] Posadas I., Monteagudo Silvia, Cena Valentinpassi, Nanoparticles for brain-specific drug and genetic material delivery, imaging and diagnosis [J]. *Nanomedicine*, 2016, 11 (7): 833 - 489.
- [15] Farmoudeh Ali, Enayatifard Reza, Saeedi Majid, et al., Methylene blue loaded solid lipid nanoparticles: Preparation, optimization, and in-vivo burn healing assessment [J]. *Journal of Drug Delivery Science and Technology*, 2022, 70: 103209.
- [16] Wasutrasawat P., Al-Obaidi Hisham, Gaisford Simon, et al., Drug solubilisation in lipid nanoparticles containing high melting point triglycerides [J]. *European Journal of Pharmaceutics and Biopharmaceutics*, 85 (3-A): 365 - 371.
- [17] Schoenitz M., Joseph S., Nitz A., et al., Controlled polymorphic transformation of continuously crystallized solid lipid nanoparticles in a microstructured device: A feasibility study [J]. *European Journal of Pharmaceutics and Biopharmaceutics*, 2014, 86 (3): 324 - 331.
- [18] Koroleva M., Portnaya I., Mischenko E., et al. Solid lipid nanoparticles and nanoemulsions with solid shell: physical and thermal stability [J]. *Journal of Colloid and Interface Science*, 2022, 610: 61-69.
- [19] Gordillo-Geleano Aldemar, Mora-Huertas E. Claudia, Solid lipid nanoparticles and nanostructured lipid carriers: A review emphasizing on particle structure and drug release [J]. *European Journal of Pharmaceutics and Biopharmaceutics*, 2018, 133: 285 - 308.
- [20] Mühlen A Z., Mehnert W, Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles [J]. *Pharmazie*, 1998, 53: 552 - 555.
- [21] Mühlen A Z, Schwarz C, Mehnert W, Solid lipid nanoparticles (SLN) for controlled drug delivery-drug release and release mechanism [J]. *European Journal of Pharmaceutics and Biopharmaceutics*, 1998, 45 (2): 149 - 55.
- [22] Müller RH, Mder K, Gohla S, Solid lipid nanoparticles (SLN) for controlled drug delivery-a review of the state of the art [J]. *European Journal of Pharmaceutics and Biopharmaceutics*, 2000, 50 (1): 161 - 177.
- [23] Mori Nitin, Navin Sheth, Ashara Kalpesh, et al., SLN brain targeting drug delivery for CNS: a novel approach [J]. *International Research Journal of Pharmacy*, 2014, 5 (9): 658 - 662.
- [24] Shi ChengYang, Li Fanglu, Cai Ying, et al., Body distribution in mice of intravenously injected camptothecin solid lipid nanoparticles and targeting effect on brain[J], *Journal of Controlled Release*, 1999, 59 (3): 299 - 307.
- [25] Luigi, Serpe Loredana, Foglietta Federica, et al., Application of lipid nanoparticles to ocular drug delivery [J]. *Expert Opinion on Drug delivery*, 2016, 13 (12): 1743 - 1757.
- [26] Burlá C, Rego G, Nunes R, Alzheimer, dementia and the living will: a proposal [J]. *Med Health Care and Philos*, 2014, 17: 389 - 395.
- [27] Saykin AJ, Wishart Heather, Rabin Laura, et al., Cholinergic enhancement of frontal lobe activity in mild cognitive impairment [J]. *Brain A Journal of Neurology*, 2004, 127 (7): 1574 - 1583.
- [28] Yiannopoulou G. Konstantina, Papageorgiou G. Sokratis. Current and future treatment for Alzheimer's disease [J]. *Therapeutic Advances in Neurological*, 2013, 6 (1):19 - 33.
- [29] Cacciatore, I., Baldassarre Leonardo, Fornasari Erika, et al., (R)- $\alpha$ -Lipoyl-Glycyl-L-Prolyl-L-Glutamyl Dimethyl Ester Codrug as a Multifunctional Agent with Potential Neuroprotective Activities [J]. *ChemMedChem*, 2012. 7 (11): 2021 - 2029.
- [30] Sozio P., D'Aurizio Eleonora, Iannitelli Antonio, et al., Ibuprofen and lipoic acid diamides as potential codrugs with neuroprotective activity [J]. *Archiv Der Pharmazie*, 2010, 343 (3): 133 - 142.

- [31] Markova, E., Taneska Lea, Kostovska Monika, et al., Design and evaluation of nanostructured lipid carriers loaded with *Salvia officinalis* extract for Alzheimer's disease treatment [J]. *J Biomed Mater Res B Appl Biomater*, 2022. 110 (6): 1368 - 1390.
- [32] Topal GR., Veszelka S., Bozkir Asuman, et al., ApoE-targeting increases the transfer of solid lipid nanoparticles with donepezil cargo across a culture model of the blood-brain barrier [J]. *Pharmaceutics*, 2020, 13 (1): 38.
- [33] Misra S., Chopra Kanvaljit, Sinha V. R., et al., Galantamine-loaded solid-lipid nanoparticles for enhanced brain delivery: preparation, characterization, in vitro and in vivo evaluation [J]. *Drug Delivery*, 2016, 23 (4): 1434 - 1443.
- [34] Zhan SM., Hpuo Dongzhi, Ping Qineng, et al., Preparation and entrapment efficiency determination of solid lipid nanoparticles loaded levodopa [J]. *Chinese Journal of Hospital Pharmacy*, 2010, 14: 1171 - 1175.
- [35] Dudhipala N., Gorre T., Neuroprotective effect of ropinirole lipid nanoparticles enriched hydrogel for Parkinson's disease: in vitro, ex vivo, pharmacokinetic and pharmacodynamic evaluation [J]. *Pharmaceutics*, 2020, 12 (5): 448.
- [36] Cometa S, Bonifacio Maria, Trapani Giuseppe, et al., In vitro investigations on dopamine loaded solid lipid nanoparticles [J]. *Journal of Pharmaceutical and Biomedical Analysis*, 2020, 185: 133257.
- [37] Cometa S, Bonifacio Maria, Trapani Giuseppe, et al., In vitro investigations on dopamine loaded solid lipid nanoparticles [J]. *Journal of Pharmaceutical and Biomedical Analysis*, 2020, 185: 133257.