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RESEARCH ARTICLE

Review on Lipid based nanoparticles for treatment of CNS diseases

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ABSTRACT

Objective(s): Central Nervous System (CNS) is one of the most important organs which is managing so many functions in human body. So, impairment of its function may results in several disorders in body, or CNS diseases, which are considered very important. CNS diseases are divided into many different groups and each group is treated with its own related medication. Some drugs that are used for treating CNS impairments have disadvantages like short length effect, renal and digestive toxicities and restrictions in pharmaceutical form. Some other drugs may cause complications worse than disease itself so the scientist shouls find the ways to solve these problems.

Methods: first "Scopus", "PubMed", and "ScienceDirect" were searched with the keywords "CNS". "CNS diseases" and "lipid based nanoparticles" and the whole articles were collected; then the most irrelevant and inappropriate articles was removed and 105 articles were remained; at the last section of article selection the best articles was selected from the 105 articles that were remained and the finally selected articles were reviewed and this article was written.

Results: The review of many important articles and summarizing them was shown that the scientists and drug designers have used many ways to overcome all or some of the disadvantages of the CNS drug delivery (as mentioned above) and they found that one of the best ways to fix these bugs is using lipid-based nanoparticles in nanotechnology field.

Conclusions: NLCs and other lipid based nano particles can use as drug carriers for CNS drug delivery if the tests and researches in the future can prove that they have no serious and irreparable risks to human's body, gene and next generations.

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INTRODUCTION

CNS, abbreviation of Central Nervous System, is one the most important body organs due to its functions and duties, and thereby each malfunctioning in CNS can cause some consequences; that is why each type of CNS disorders should quickly diagnose and treat. CNS diseases are divided into different categories including neurodegenerative diseases, part of them are related to many different factors such as oxidative stress and glutamate,apoptosis, aging, and etc. This kind of diseases cover many CNS diseases, among them Alzheimer, Parkinson and Huntington will be discussed in this article. The next group is infectious diseases, causing overwhelming inflammation in brain and other parts of CNS. One of the most important diseases in this group is cerebral malaria resulting to unpleasant complications and even death, especially in children. Traumatic disorders,

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brain cancers and tumors, autoimmune-based CNS disorders and immunodeficiency are other types of CNS diseases that are caused by traumas (especially child hood traumas), genetic disorder, some types of viruses, and more other causes. There are many ways to cure these disorders, but each of them has its own disadvantages. So, researchers are trying to find new ways to overcome these disadvantages; among them nanoparticles may be desirable, [1,2] covering a broad range of applications in treatment of many kinds of CNS disorders, from cerebral malaria [3] to AIDS. The nanoparticles that are used in CNS disorders treatment, have a huge variation and only the Lipid-Based Nanoparticles (LBN), including NLC, SLN, and LB nanoemultions will be discussed in this article.

Lipid based nanoparticles

Different types of nanoparticles have different applications spectrum, from using as silver nanoparticles for antimicrobial coating to using as tattoo inks!.[4] In his regard, one of the newest types of nanoparticles are lipid-based nanoparticles that have been used for a variety of purposes, some of which are discussed in the following.

SLNs

Solid Lipid Nanoparticles (SLNs) have discovered in the late years of the last century to overcome the shortage of previous nanoparticles like polymeric nanoparticles, liposomes and etc. This kind of nanoparticles are made of solid lipids at ordinary temperature. SLNs have a solid core coated with monolayer phospholipids and the drugs are entrapped in solid core. These nanoparticles are used in many different medical purposes such as controlled drug delivery, cosmetic, dermatologic preparations and etc.

NLCs

Nanostructured Lipid Carriers (NLCs) are a kind of lipid-based nanoparticles that are very similar to SLNs with similar applications. The most significant difference between NLCs and SLNs is that NLCs are made by mixing of solid lipids and liquid lipids, resulting to improved drug loading, particle capacity and release properties.

Micro and nanoemulsions

These kinds of lipid-based nanoparticles are the mixture of oil, surfactants and water, making it one of the best choices for hydrophobic drugs delivery.[5] These kind of nanoparticles are used in several cases, some of them will be discussed in this article.

Liposomes

Bilayer vesicle with empty middle, this is the liposomes definition,[6] the nanoparticles that are used for medical usages like targeted drug delivery with properties including enhanced drug uptake and prolonged drug circulation in blood and also the capacity to gene transfer.

CNS diseases and lipid based nanoparticles

Using nanoparticles is one of the newest methods for treating CNS diseases and there has been many research on this method, among which some cases using lipid particles will be discussed at the following.

CNS infectious diseases

Infectious diseases can be caused by a large variety of organisms, from simple viruses to complex organisms like malarial parasites. The efficacy of lipid-based nanoparticles for treating this kind of CNS diseases has been shown successfully.[7, 8]

Malaria is a parasitic disease in the category of CNS infections. A study investigated the effect of Artemether (ARM) + Lumefantrine (LFN) carried by Nanostructured lipid carriers (NLC) made by oleic acid+glycerylin. *In vitro* & *In vivo* tests were performed in PBS buffer on Swiss Albino mice, C57BL/6 mice and albino Wistar rats. The experimental results in the buffer environment showed that both drugs were amorphous and had sustained release. The presence of NLCs increased the stability up to 6 months at various temperatures and humanity, and for 1 year at stable temperature. The use of NLC loaded by ARM and LFN as an intravenous injection in Swiss albino mice indicated that the time life after infection increased by 45 days. On the other hand, the mice were treated by 1/100 of oral ARM-LFN NLC combination. In the study, treatment of C57BL/6 mice had successful outcome, with the results such as complete resolution of symptoms, rectal normal temperature restoration in the 4th treating day, and finally no toxicity and side effects were observed in albino Wistar rats in 14 days of treatment.[9]

Brain cancers & tumors

Cancers can happen by genetic failures; these failures can be the congenital malformation or the result of some other reasons, smoking, some kinds of infections and viruses.[10]

Table 1. Lipid based nanoparticles which are used in treatment of CNS diseases and their mechanism of action

Disease category	Disease name	Drug	Carrier	In vitro/ in vivo	Cell line (Invitro environment)/ animal	Results of using nanocarrier	Reference
CNS Infectious diseases	Cerebral malaria	Artemether + Lumefantrine	NLC	*In vitro* & *In vivo*	PBS buffer	- Sustain releasing of both drugs. - Amorphization of both drugs. - Increasing stability up to six months for both drugs in different temperature and humanity. - Increasing stability for both drugs up to one year in stable temperature.	9
					Swiss albino mice (for non-CM treating)	- Increasing life time after infection up to 45 days. - ARM-LFN combination to treat the mice was reduced to 0.01.	
					C57BL/6 mice (for CM treatment)	-Rectal temperature becomes normal 4 days after treatment. -The symptoms of cerebral malaria was completely eliminated.	
					Albino wistar rats	- No toxicity & adverse effects in the rats following 14-day treatment.	
Brain cancers & tumors	Brain cancer	Curcumin (Cur)	NLC	*In vitro* & *In vivo*	1human brain cancer cell (A172)	- Inhibition effect is significantly enhanced (IC50<20 mg/mL). - ROS levels were increased at 20mg/mL concentration of Cur and NLC-Cur but only NLC-Cur can increase the ROS level at 10 mg/mL. - NLC formulation improved the induction effect of Cur.	12
					BALB-C female mice	- NLC-Curcumin can inhibits the growth of BALB-C mice bearing A172 xenografts.	
Brain cancers & tumors	CNS histone hyperacetylation	Curcumin	NLC	*In vitro* & *In vivo*	PBS	- An initial effect at the 4–5 h after prescription and the sustained release at the remaining time.	11
					Male CD1 mice	- Decreased histone acetylation in CNS.	

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Brain cancers & tumors	Glioblastoma	Ferulic Acid(FA) &Idebenone (IDE)	NLC & SLN	*In vitro*	Cellulose membranes which are made of Franz diaphragm diffusion cells	- The FA release rate is better controlled in NLCs with the higher percentage of oil, comparable to SLN observations.	14
					Human glioblastoma cancer U87MG cells	- No cytotoxic effects was shown from MTT bioassay and caspase-3 cleavage. - Glioblastoma can be treated by using FA loaded NLC.	
						- The effect of FA loaded NLCs in treatment of cells is better than IDE or IDE loaded NLCs.	
Neurodegenerative disorders	Alzheimer	Curcumin	NLC	*In vitro, ex vivo& In vivo*	1% (w/v) tween 80 in Physiological saline 181	- The drug diffusion from NLC is limited by Lactoferine adsorption.	22
					Brain capillary endothelial cells (BCECs)	- NLC and Lf-mNLC was shown no toxic effects on BCECs.	
					ICR mice & Sprague-Dawley (SD) rats	- Flexible drug delivery platform can be provide in brain targeting with successful BBB cross of Lf-mNLC.	
Neurodegenerative disorders	Neurodegenerative diseases (intranasally administering)	Nile Red and DiR	Chitosan Coated NLC	*In vivo & In vitro*	Human bronchial epithelial(16HBE14o-) cell line	- Effective delivery to the brain.	23
					C57 mice	- No fibrosis, atopic tissue and inflammatory was shown.	
Neurodegenerative disorders	Huntington	Brain-derived neurotrophic factor (BDNF)	Nanoscale carriers for encapsulation	*In vivo*		- The potentiation of the drug's medical activity has proven this method.	17
Autoimmune based CNS disorders	Amyotrophic lateral sclerosis (ALS)	Minocycline	Minocycline loaded nanoliposomes and nanoparticles	*In vivo*	Nanoparticles and nanoliposomes which are loaded with Minocycline	- The degenerative gene in familial ALS (Cu /Znsuperoxide dismutase) can be delivered efficiently in this method.	17

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Neurodegenerative disorders	schizophrenia	Aripiprazole	Nanoemulsions	*In vivo*		- The needed dose and side effects was reduced because of the Improvement of drug BBB penetration, drug solubility and bioavailability.	17
Other CNS diseases	Insomnia	Zaleplon	Nasal nanoemulsion gel	*In vivo*		- Enhanced bioavailability and improved tissue permeation.	17
Neurodegenerative disorders	Alzheimer	Ferulic acid	NLC & SLN			- Increasing bioavailability	40
		Galantaminehydrobromide SLNs	NLC & SLN		Cognitive deficit rats	- Significant capability of memory restoration and 100% bioavailability enhancement.	
		Lipoyl-memantine co-drug loaded SLNs	NLC & SLN	*In vitro*	Mouse N2a neuroblastoma	- The method proved to be not toxicological and cytotoxic.	
		rivastigmine loaded SLNs	NLC & SLN			- Enhanced *ex vivo* diffusion.	
		Donepezil	Nanoliposomes		Healthy male Wistar rats	- The brain bioavailability of donepozil was increased so much by intranasal administration of these liposomes. - The safety of method was proved.	
		Rivastigmine	Nanoliposome		Rat models with AD	- The concentration of Rivastigmine in hippocampus and cortex was significantly increased when the drug administrated with the liposomes.	
		Galantamine	Nanoliposome			- Intranasal administration was greatly enhanced the inhibitory effect of acetylcholinesterase. - The cytotoxic was noticeably diminished.	
		Curcumin-conjugated monoclonal antibody	Nanoliposome	*In vitro*	Transgenic mice's hippocampus and neocortex	- Was shown significant amounts of labeled Aβdeposits.	

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		Anti-transferrin receptor antibody	Nanoliposome	*In vitro*	hCMEC/D3 cells	- Non-decorated liposomes have Lower permeability across the BBB model in comparison to nanoliposomes.	
		Cell-penetrating TAT peptide and polprotein peptide analog	Nanoliposome	*In vivo*	APP/PS1 mice	- Plasma's Aβ level was increased.	
		Curcumin	Nanoemultions	*In vitro*	Sheep nasal Mucosa	- The formulations were shown no toxicity. - Highest flux.	
		Curcumin and resveratrol	Nanoemultions	*In vivo*	Albino rats	- Repeated administration cause no damage and destruction to lining epithelium of nasal cavity.	
		*Centellaasiatica*plant extract	Nanoemultions	*Ex vivo*		- Infiltrate.	
				In vivo		- Antioxidant effect.	
		Rivastigmine	Microemultions		Nasal ciliotoxicity for intranasal administration	- stable for three months	
		ligustrazine phosphate (LP) and Huperzine A	Microemultions	*In vivo*	Male Sprague–Dawley rats	- Progression of AD was suppressed by increasing in the cerebral cholinergic function and oxidative systems.	
					Amnesia rats	- After transdermal administration also confirmed in scopolamine induced.	
Other CNS diseases	Schizophrenia	Olanzapine/ Simvastatine	NLC	*In vitro & In vivo*	Newborn pig epiderm	- Skin permeation	42
					PBS	- Release studies with a diffusion area for 48 hours	
					Combo- NLC	- Zeta potential is similar, particle's mean size is lower and polydispersity is higher. - Simvastatin was released lower than Olanzapine. - Simvastatin is more solvable in the solid lipid tripalmitin and Olanzapine is more solvable in oleic acid as a liquid lipid.	
					Rat	- Equal permeation for both drugs.	

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Disease category	Disease name	Drug	Carrier	In vitro/ in vivo	Cell line (Invitro environment)/ animal	Results of using nanocarrier	Reference
Neurodegenerative disorders	Parkinson	Bromocriptine (BC)	SLN & NLC	*In vivo*	Sprague-Dawley rats	- BC and BC–NLC have activity at 30 min after administration, but the effect was end only 3h after administration for BC and was continuous 3 and 5 hours after administration for BC–NLC. - Antiparkinsonian activity only for free BC after 30 min. - Immobility time was reduced with BC. - Akinesia was reduced with both BC and BC–NLC. - BC cause shorter therapeutic time interval in compare with BC-NLC.	25
Neurodegenerative disorders	Parkinson	L-DOPA (PD)	NLC	*Invitro*	Characterization	- Prescribed dose was reduced because of the solubility improvement of PD and protection of that from plasma esterases and increasing its half-life. - The effect of lipases on PDB-NLCs and PDC-NLCs was very similar.	24
Brain cancers & tumors	Brain tumor	Paclitaxel (PTX,Anzatax)	NLC	*In vitro*	Characterization	- The drug loading of NLCs ranged from 4.3% to 9.8%. - CremophorVR EL is more toxic than empty NLCs; AnzataxVR and free PTX is more toxic than the empty NLCs too.	15
						- Free PTX was less toxic than AnzataxVR. - The inhibiting activity of Tf-PTX-NLCs increased with increasing in PTX concentration.	

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Disease category	Disease name	Drug	Carrier	In vitro/ in vivo	Cell line (Invitro environment)/ animal	Results of using nanocarrier	Reference
Immunodeficiency disease	HIV in CNS	Efavirenz	NLC	*In vitro & In vivo*	PBS	- 92.45% of the drug was released at first 24 h.	19
					Male Wistar rats	- The therapeutic levels of drug was increased in CSF with intranasal administration because of surpassing the BBB.	
					Blank brain tissue	-The brain tissue wasn't damaged with repeated administration of formulation.	

CNS Histone Hyperacetylation is one of the subsets of brain cancer and in a study the results of examining the curcumin-NLC on PBS and Male CD1 mice was indicated. NLC particles were made by Glyceryl palmitostearate as solid and Capric triglycerides as liquid lipid. Initial burst effect for the first 4–5 h and sustained release of drug for the remaining time of monitoring were shown in PBS and decreasing CNS histone acetylation in CD1 mice.[11] Examining the effects of Tripalmitin + oleic acid-made NLCs that were loaded by curcumin (Cur) in *in vitro* studies on human brain cancer cells showed that both Cur and NLC-Cur caused increasing in ROS at 20 mg/mL concentration and NLC-Cur can do it at lower concentration (10 mg/ml) too. By the way, the apoptotic induction effect of Curcumin becomes better by using this formulation. *In vivo* studies on female BALB-C mice showed that the growth of mice bearing A172 xenografts was inhibited by Curcumin loaded NLCs.[12] In another study, two carriers, NLC and SLN, were examined to increase the effect of Ferulic Acid (FA) & Idebenone (IDE) in glioblastoma, disease from the category of brain cancer and tumors which is one of the most dangerous brain tumors that is hard to cure and is most fatal brain tumors exactly in elder patients[13]. Cellulose membranes which are made of Franz diaphragm diffusion cells was examined *invitro* and it is observed that FA release was better when carried by more oil containing NLC formulations than when carried by SLNs. Experiments on human U87MG cells had acceptable results with no cytotoxic effects; it was proved that treatment with IDE or IDE-loaded NLCs have lower effect than FA or NLCs loaded with FA and it was showed that FA-NLC could be a potential treatment for glioblastoma.[14] A review of paclitaxel-loaded NLCs in *in vitro* environment showed that the drug loading of NLCs ranged between 4.3 and 9.8% and empty NLCs were less toxic than free paclitaxel and anzatax® and also anzatax® was more toxic than paclitaxel. Also, it was realized that the inhibiting activity of transferrin-conjugated paclitaxel NLCs (Tf-PTX-NLCs) was improved by increasing the PTX concentration. NLCs, in this study, were made by triolein(liquid) and Cholestrol (solid).[15]

Autoimmune based CNS disorders

Autoimmunity includes a group of diseases that are caused by an impairment of the immune system like some kinds of cancers and multiple sclerosis (MS) with very serious complications in patients.

Amyotrophic lateral sclerosis (ALS) is a disease that can be caused by gene mutations and often called Lou Gehrig's disease. This illness can cause unbearable disabilities by destroying nerve cells. [16] A research on ALS with minocycline loaded nanoliposomes showed that using nano liposomes resulted in improvement of minocycline delivery to Cu/Zn superoxide dismutase gene,[17] the gene that its mutation refers to familial ALS.

Immunodeficiency

One of the most important causes of immunodeficiency is human immunodeficiency virus (HIV) with various types like cyanovirin-N. It was discovered that at 1981 for the first time at USA, [18] this virus cause a venereal disease (AIDS) which is transmitted from sex with an infected person.

The *in vitro* study of Efavirenz (Efa) with NLC & SLN in PBS environment showed 92.45% of drug releasing at 24 hours. Study on blank brain tissue showed that Efa-NLC had no damage on the brain tissue on low and medium dose repeated administration and caused no toxic effects in these doses. On the other side, administration of formulation through intra nasal route caused significant drug concentration in the cerebrospinal fluid (CSF) by passing through the Blood Brain Barrier in male Wistar rats *in vivo*.[19]

Neuro degenerative disorders

Neurodegeneration can cause by loss of neuron structure or function of like neurons death and etc.

and this category includes many kind of diseases like Parkinson, Alzheimer and Huntington.[20,21]

A study tried to investigate the effect of an encapsulated Brain-derived neurotrophic factor (BDNF) with nanoscale carriers on Huntington's disease. In an *in vivo* analysis, it was found that the strategic therapeutic effect of this method is important.[17] A study examined the encapsulation of Aripiprazole with Nano-emulsions and its effect on schizophrenia. *In vivo* results indicated that the needed dose and the side effects were reduced because of the improvement of drug's bioavailability, solubility and BBB penetration;[17] Another study proved that the effect of curcumin carried by Nanostructured Lipid Carriers (NLCs) was evaluated on Alzheimer disease. *In vitro* studies on 1% (w/v) tween 80 in Physiological saline 181, found that the drug release from NLCs was decreased by

Lactoferine (Lf) adsorption, and *in vivo* studies on Brain capillary endothelial cells (BCECs) showed that empty NLCs and Lf-modified NLCs caused no toxicity on BCECs. On the other hand, curcumin-NLCs were examined on Sprague-Dawley (SD) rats & ICR mice and showed that the flexible drug delivery platform can be registered because of Lf-mNLC successful BBB crossing during the brain targeting.[22] In a study, intranasally administering of Nile Red and DiR carried by chitosan coated NLCs (Miglyol + Precirol ATO5) was evaluated in Neurodegenerative disorders therapy. In this study, *in vitro* experiments on human bronchial epithelial (16HBE14o-) cell line showed effective delivery to the brain and in *in vivo* studies on C57 mice showed no inflammatory, fibrosis and atopic tissue formation.[23] One of the important choices of Parkinson's disease treatment is L-dopa (LD). However one of the most important complication of long-term LD therapy is due to its metabolism. *In vitro* studies showed that Levodopa loaded NLCs needed less prescribed dose. It was because of several reasons: its solubility was improved, NLC formulations protected LD from metabolism and especially from esterase enzymes of plasma, which could increase the drug's half-life and it is necessary to ensure that the effect of lipases is so similar in PDB and PDC NLCs.[24] Bromocriptine (BC) is a agonist of dopamine receptors with a wide therapeutic potential in neurodegenerative disorders. *In vivo* studies proved that the effect of BC loaded NLCs had longer lasting therapeutic benefit than free BC after administration in male Sprague-Dawley rats in Parkinson's disease therapy. Both formulations elevated the effect at first half an hour after administration. The effect of free BC disappeared after 3 h, while the effect of NLC-BC continued by 3-5 hours after administration. Both formulations significantly showed a reduction in akinesia at the first half an hour after administration and also BC could reduce the immobility time. Also, both free BC and NLC-BC formulations proved to reduce the immobility time.[25] Alzheimer is another neurodegenerative disorder. Gastrointestinal side effects of current Alzheimer's FDA approved drugs lead to drug therapy discontinuation and different studies evaluated the using of nanotechnology in drug delivery of Alzheimer's therapy. It was reported that intravenous administration of nano encapsulated ferulic acid lead to increased bioavailability. In an *in vivo* study, galantaminehydrobromide SLNs was administered orally in cognitive deficit rats. This formulation enhanced bioavailability up to 100%, compared to free galantamine and significantly showed capability of memory restoration.[26] In another research, the inhibitory effect of galantamine on acetylcholine esterase was greatly enhanced by galantamine flexible liposomes intranasal administration, and the cytotoxicity was significantly reduced.[27] An *in vitro* study used SLNs loaded with lipoyl-memantine as a co-drug in mouse N2a neuroblastoma; This study proved safety of the formulation from toxicological point of view and suggested its potential for in vivo investigations.[28] In another study, Rivastigmine-loaded liposomes was used for intranasal application. The average SLN rivastigmine concentration was significantly higher compared to free rivastigmine in hippocampus and cortex of ret models with AD.[29] Also, using Rivastigmine-microemulsion as an intranasal administration for nasal ciliotoxicity was stable for three months.[30] Intranasal administration of donepozil loaded nanoliposomes increased the bioavailability of donepezil in healthy male wistar rats and furthermore the safety of formulations was approved.[31] In a study, conjugated monoclonal antibodies (mAbs) with liposomes was used to targeted drug delivery across the BBB, Curcumin-conjugated mAbs-nanoliposomes was injected into the transgenic mice's neocortex and hippocampus of and showed the specific binding to Aβ deposits.[32, 33] In an *in vitro* investigation, using apolipoprotein peptide analog, TAT peptides and anti-transferrin receptor antibody in hCMEC/D3 cells, showed higher permeability across the barrier model. These formulations were used for *in vivo* studies on APP/PS1 mice and showed increased plasma level of Aβ.[34, 35] Also, curcumin nanoemulsion was investigated in sheep nasal mucusa as an *in vitro* study which proved the safety and highest flux of formulation across mucosa.[36] In another *in vivo* study, Albino rats were received the nanoemulsion of curcumin and resveratrol. The toxicity results showed the lining epithelium of nasal cavity doesn't damaged with repeated administration of both formulations and in addition both of them can reach the therapeutic concentration in the brain.[37] *Centellaasiatica* plant extract was used to prepare a nanoemulsion for intranasally delivery and showed ex vivo permeation and also *in vivo* antioxidant property.[38] In this article, a bioadhesive microemulsion-based patch loaded with huperazine A and ligustrazine phosphate

(LP) was used for transdermal drug delivery. *In vivo* studies on male Spargue-Dawley rats showed reduced progression of Alzheimer disease because of improved cerebral cholinergic function and oxidative system. In scopolamine-induced amnesia rats all of these effects were visible.[39,40]

Other CNS diseases

Some types of CNS diseases cannot be categorized in the categories that were said above, like insomnia, the diseases caused by some drugs age-related diseases, and schizophrenia, which all have many reasones.

Schizophrenia is caused by genetic and environmental factors[41] and the most important symptoms of this disorder are hallucination (especially vocal illusions), delusion and disorganizing in thinking and speech. So, many drugs are used for treating schizophrenia and using nanotechnology can improve their effect. In a study, it was shown that treating with Olanzapine- and Simvastatine-loaded NLCs in PBS causes gradual release up to 48 hours and skin permeation was observed on newborn pig's skin. *In vivo* examination of this nanoparticles on rats showed equal permeation of both drugs. Also, it was proved that conventional NLCs have higher mean particle size, lower polydispersity and similar Z-potential compared to combo-NLCs. Olanzapine was more soluble in Oleic acid (liquid part of NLCs), while Simvastatin was more soluble in Tripalmitin (solid part of NLCs) and the releasing extent of Simvastatin is lower than Olanzapine.[42] Other *In vivo* research on treating insomnia showed that nasal delivery of Zaleplon with nanoemulsion gelscauses enhanced tissue permeation and bioavailability.[17]

CONCLUSION

In general it can be concluded that lipid-based nanoparticles can be introduced as one of the best types of nanoparticles for using in the treatment of CNS disorders through solving many problems such as passing medications from BBB, drugs instability in Gastro Intestinal tract, Protect drugs from unwanted metabolisms and etc.

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AUTHORS CONTRIBUTIONS

All of the authors involved in all sections of the paper (from A to Z) and therefor, they will contribute to all rights and results of the publication of the article.

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