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NANOSTRUCTURED LIPID CARRIERS ACTING ON CENTRAL NERVOUS SYSTEM

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Abstract: The central nervous system, or CNS for short, is among the most significant bodily organs because of what it does for the human body. Therefore, a decline in its function may lead to a variety of maladies of the CNS or other body systems that are highly significant. Drug delivery technologies based on lipids called nanostructured lipid carriers (NLCs) have received much study. The creation of NLCs, or nanostructured lipid carriers, was done. The diverse delivery methods for nano-based systems include parenteral, transdermal, ophthalmic, oral, and topical. The creation of NLCs included blending spatially incompatible liquid and solid lipids. Improved bioavailability and higher solubility are drug therapy's key benefits over traditional carriers of NLCs. NLCs used for brain targeting NLCs for CNS diseases (glioma/brain cancer, ischemic stroke, Alzheimer's disease, Parkinson's disease, epilepsy, migraine, Hodgkin's disease, schizophrenia, and multiple sclerosis) are discussed in this review along with their benefits and drawbacks. NLCs method, the most common categories include imperfect, amorphous, and multiple types. Solid lipids, liquid lipids, surfactants, and other excipients are also employed in NLCs. The methods used to create NLCs include high-pressure homogenization, solvent emulsification/evaporation, micro-emulsification, ultrasonication, supercritical fluid, and solvent injection. In recent years, it has drawn more and more interest.

Keywords: **CNS disease, Nanostructured lipid carriers, Liquid lipid, Solid Lipids, Drug delivery, Methods,**

I. INTRODUCTION

Nanostructured lipid carriers are the nanocarriers that have the lowest time between invention and commercialization. Muller first developed NLCs in late 1999, and the Dr. Rimpler Company in Germany introduced two cosmetic products, Nanorepair Q10 serum, and Nanorepair Q10 cream, to the market in 2005 [Jingyuan Wen *et al*,2018]. Nanostructures are particles with diameters ranging from 10 to 1000 nm that absorb or attach to drug molecules that are dissolved or entrapped. NLCs have efficient qualities. NLCs are the second generation of lipid nanocarriers [Asha Spandana *et al*,2020] consisting of a matrix containing both solid and liquid lipids [Chandana Karnati *et al*.,2019]. Additionally, the bioavailability, drug loading, and solubility of the drug in various situations and environments are all improved by this particular form of NLC nanostructure. The physical and chemical characteristics of NLC particles remain stable [Amita Sharma *et al*,2018]. Drug delivery technologies that are nanostructured or nanoparticulated are becoming increasingly important and well-liked on a global scale. have been evaluated as very promising carriers for parenteral, transdermal, and oral drug administration over the past ten years [Bhupinder Singh *et al*,2018]. The shortcomings of SLNs were addressed by the introduction of NLCs. An unstructured matrix comprised of a combination of solid and liquid lipids was used in place of an ordered structure of SLNs to improve a carrier's qualities [JanSobczy´nski *et al*,2019].

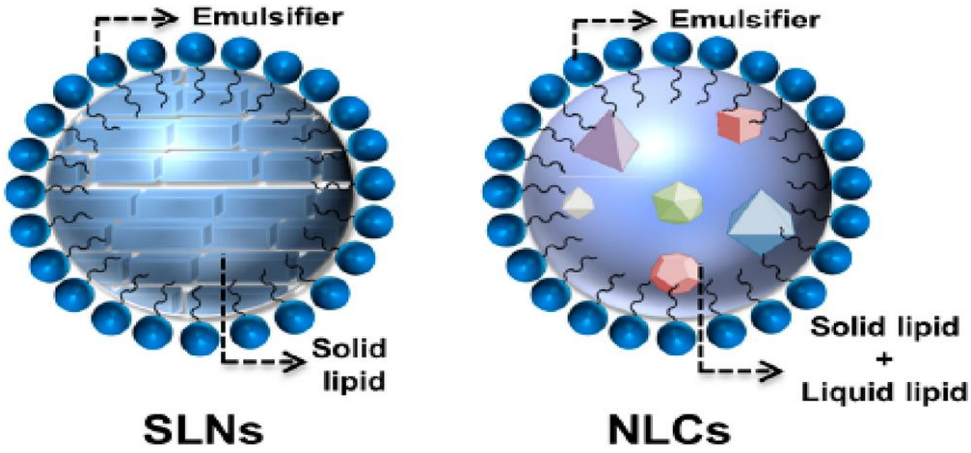

Figure 1. A schematic illustration of nanostructured Lipid Carrier (NLC) and solid lipid nanoparticles (SLN) [Heshu Rahman *et al*,2020]

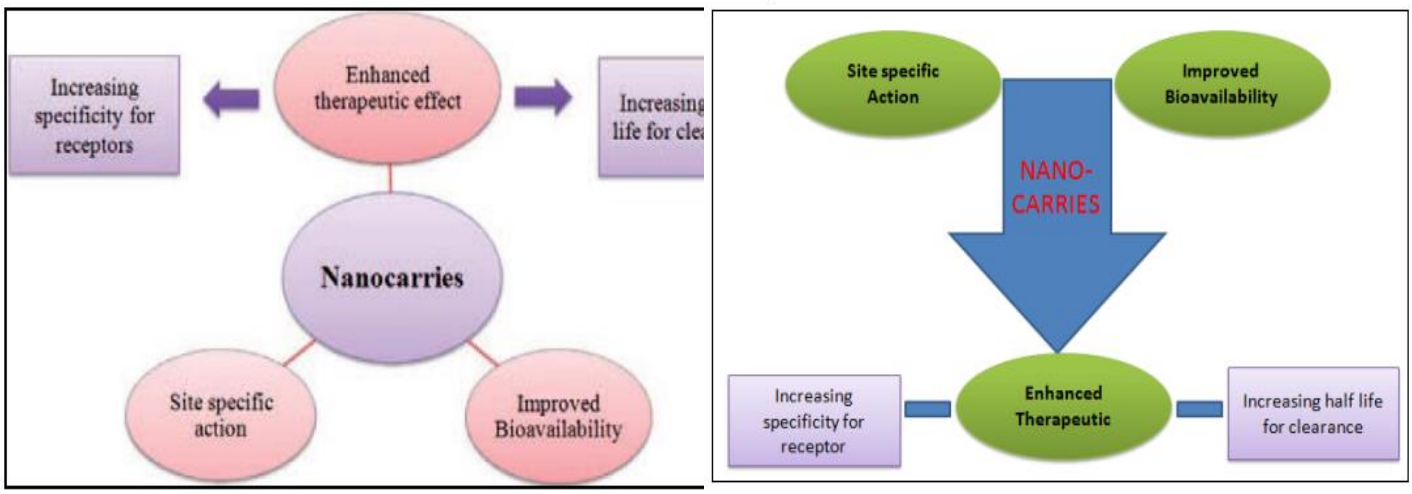

Figure 2. Important aspects of nanocarriers [Shishu Pal *et al*,2020]

II. TYPES OF NLCS

There are various NLC varieties that vary according to the lipid mixture's composition and the method of manufacturing [Samar Faheim *et al*,2018].

NLCs type I

Because of their unstructured matrix, they are also known as imperfect crystal kinds. These flaws allow for easy drug insertion and have a high degree of entrapment effectiveness [Khushboo Pathania *et al*,2022]. Glycerides are one of the various fatty acids that can be employed to enhance and modify the structure. The overall amount of structural flaws are both responsible for and beneficial for the ability of a good drug to have an easily enhanced property. By combining lipids that are spatially dissimilar, which might result in flaws in the crystal lattice, type I of NLCs can be created. This problem can be solved by utilizing the tiny quality of glycerides [Amit Sharma *et al*,2018].

NLCs type II

It is sometimes referred to as Multiple type NLCs. It is an oil, lipid, and water kind. Drugs that are lipophilic are more soluble in liquid lipids than solid lipids. This concept results in the development of many types of NLC of its solubility causes phase separation, creating tiny oil nano compartments ringed by a high liquid lipid concentration. Low quantities of oil moieties are efficiently distributed in the lipid matrix. The oil that is added in excess of the solid matrix. High drug entrapment effectiveness, regulated drug release, and reduced drug leakage are benefits of the Type II paradigm [Iti Chauhan *et al*,2020].

NLCs type III

They are also known as amorphous kinds and are made by carefully combining particular types of solid and liquid lipids (eg, Isopropyl myristate). Lipids are blended in this to stop them from crystallizing. The solid, amorphous lipid matrix is composed of lipids. Drug ejection caused by crystallization is prevented by the absence of crystallization. Water-soluble medicines were coupled with lipids to create a water-insoluble lipidic conjugate in a further variant of the lipid matrix. To create a lipid drug conjugate (LDC) nanoparticle, the lipid conjugate powder was melted and treated in the same manner as the other varieties. Salt formation or covalent bonding are two methods of conjugation. [Amandeep *et al*,2019]

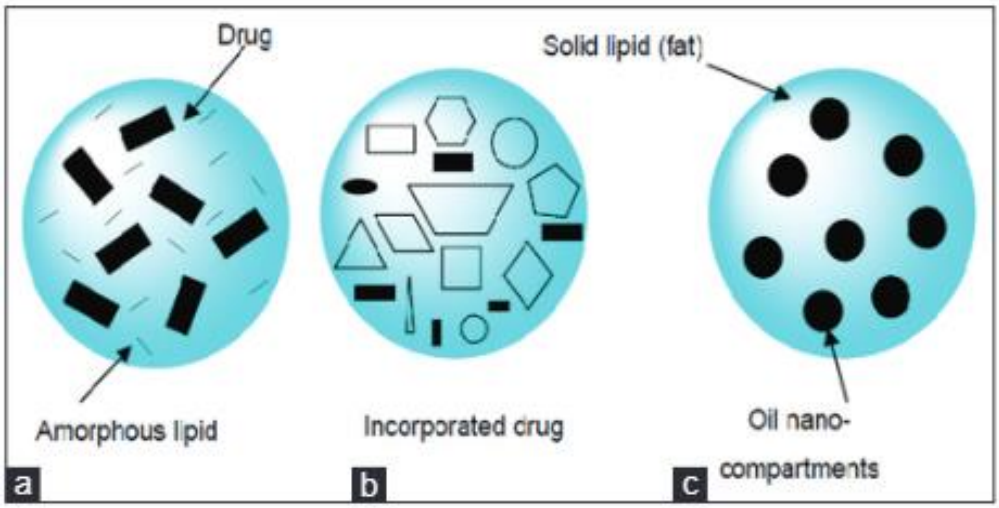

Figure 3. Types of NLCs: (a) Amorphous type, (b) highly imperfect, (c) multiple O/FW type [Dhruv Purohit *et al*,2016].

III. NLCS FORMULATIONS

Materials for NLCs

Solid lipids, liquid lipids, surfactants, and surface modifiers are the main NLC constituent. The NLCs' solid lipid core is made up of solid lipids, which also serve to create the matrix. Different solid lipids with their respective melting points and compositions are used in the NLC formulations. Liquid lipids (oils), on the other hand, are the lipophilic excipients that are utilised to integrate the solid lipid core and to lessen its crystallinity. The majority of the medications are dissolved in synthetic oils, which are used to prepare NLCs. Natural oils can also be employed. Various types of synthetic and natural oils used in the creation of NLCs, along with examples of each.The third component surfactant, which is frequently a polymeric substance, stabilises the lipid crystal suspension, maintains uniform PS distribution, and inhibits particle development. Surfactants are essential in the production of formulations since they affect several NLC properties, including viscosity and water-solubilizing ability. The surface modifiers, which are the components that contribute unique features to the formulation and affect the in vivo effects of NLCs, are another significant part of NLCs [Shamama Javed *et al*,2022].

In NLCs, a surfactant or combination of surfactants is present in the aqueous phase as well as the unstructured solid lipid matrix, which is composed of a blend of solid and liquid lipids. While the surfactant content ranges from 1.5% to 5% (w/v), solid lipids and liquid lipids are often combined in a 70:30 to 99.9:0.1 ratio [Ana Beloqui *et al*,2016].

Table 1. List of solid lipids, their melting points, and compositions used in the NLC formulations [Shamama Javed *et al*,2022].

Solid lipids	Melting point (±5°C)	Compositions used
Stearic acid/octadecanoic acsssssssid/ cetylacetic acid	69.6	Stearic acid + palmitic acid + small concentration of oleic acid (HLB value = 15)
Glyceryl monostearate (GMS)	57–65	Monoglycerides + diglycerides of fatty acids (HLB value = 3.8)
Glyceryl monostearate polyoxylethylene stearates (Gelot™ 64)	55–62	Mixture of glycerol monostearate and PEG-75 (MW 3,500) stearate (C18) (HLB value = 10)
Carnauba wax	82	Hydroxy acid aliphatic ester + p-methoxy cinnamic acid aliphatic ester + p-hydroxy cinnamic acid aliphatic diester + oxy-polyhydric alcohol (HLB value = 12)
Cetyl palmitate	54	Ester derived from hexadecanoic acid and hexadecanol (HLB value = 10)
Glyceryl palmitostearate (Precirol® ATO 5)/ glyceryl distearate	50–60	Mono- + di- + triglycerides of C16 and C18 fatty acids (HLB value = 2)
Glyceryl behenate (Compritol® 888 ATO)/ glycerol dibehenate	65–77	Mono- + di- + triesters of behenic acid (HLB value = 2)
Compritol® HD5 ATO/behenoyl polyoxyl-8 glycerides	60–67	Mono- + di- + triglycerides of PEG8 and mono- + diesters of behenic acid (HLB value = 5)
Geleol™ mono- and diglycerides NF/monoand diglycerides	54–64	Mono- + di- + triesters of palmitic acid (C16) and stearic acid (C18) (HLB value = 3)
Grades of Softisan – it is a mixture of triglycerides graded based on even-numbered, saturated, and non-branched natural fatty acids of chain length C8–C18 and are of vegetable origin		
Softisan 100	33–35	Hydrogenated co-glycerides + mixture of C10–C18 fatty acid Triglycerides
Softisan 154	53–58	Hydrogenated palm oil + mixture of C10–C18 fatty acid triglycerides
Softisan 142	42–44	Mixture of C10–C18 fatty acid triglycerides of
Softisan 138	NA	Mixture of C10–C18 fatty acid triglycerides and diglycerides
Softisan 645	NA	Mixture of diglycerol with caprylic, isostearic, capric, stearic, and adipic acid
Softisan 378	38	Mixture of caprylic/capric/myristic/stearic triglycerides
Softisan 601	40–45	Hydrogenated coconut oil + ceteareth-25 + triglycerides (glyceryl cocoate)
Softisan 649	35	Mixture of diglycerol, caprylic, isostearic, capric, stearic acid, hydroxystearic, and adipic acid
Grades of Witepsol® –synthetic hard wax, available in different series		
Witepsol®H (5,12,15,19,32,35,37)	31–38	Mixture of triglycerides + diglycerides (15%) + monoglycerides (1%) with low hydroxy value
Witepsol® W (32,25,35,45)	32–35.5	Mixture of triglycerides (65–80%) + diglycerides (10–35%) + monoglycerides (1–5%) with high hydroxy value
Witepsol® S (51,55,58)	30–35.5	Non-ionic ethoxylated emulsifier
Witepsol® E (75,76,85)	37–44	Series E are hard fats having melting point more than the body temperature
Imwitor grades		
Imwitor 372P	62	Glyceryl stearate citrate, HLB = 12
Imwitor 491	66–77	Mixture of GMS and monoglycerides with HLB value 4
Imwitor 900K	61	Glycerol monostearate (40–55%, type I), HLB = 3
Imwitor 928	34	Mixture of glyceryl cocoate and medium-chain partial glycerides
Dynasan grades		
Dynasan® 116	63–68	Tripalmitin
Dynasan® 118	72	Glyceryl tristearate/triglycerides

Dynasan® 114	55–58	Solid triglycerides (triglycerides/trimyristin)
Others		
Lauric acid (dodecanoic acid)	43.2	Mixture of saturated fatty acid with a 12-carbon atom chain
Apifil ® CG/PEG-8 Beeswax	59–70	It is a polar beeswax derivative by esterification of beeswax with polyethylene glycol (PEG). PEG group imparts hydrophilic properties to beeswax.
Tefose® 63	49	Mixture of ethylene glycol palmitostearate + PEG-6 palmitostearate + PEG-32 palmitostearate (HLB value = 9.5)
Tristearin/glyceryl tristearate	54–72	It is derived from three units of stearic acid

Table 2: Synthetic and natural oils used for the formulation of NLCs with their examples [Shamama Javed *et al* ,2022].

Types of oil used	Examples
Synthetic oils	
Medium-chain mono- and diglycerides of caprylic/ capric acid	Capmul MCM, Imwitor
Propylene glycol (PG) fatty acid esters including PG monolaurate	Lauroglycol FCC, Capmul PG-12, Lauroglycol 90
PG diester of caprylic/capric acid	Labrafac PG
PG dicaprylate	Miglyol 840
Medium-chain triglycerides and their esters including capric/caprylic triglycerides	Akomed R, Akomed E, Miglyol 810, Captex 355, Crodamol GTCC, Neobee M5
Fractionated coconut oil	Miglyol 812, Triacetin, Labrafac CC, Captex 300
Long-chain monoglycerides, such as glyceryl monolinoleate	Maisine 35
Glyceryl monooleate	Peceol, Capmul GMO
Capric/caprylic/diglyceryl succinate	Miglyol 829
Fatty acids, such as oleic acid and caprylic acid	Crossential O94
Fatty acid esters	Ethyl butyrate, ethyl oleate (Cardamol EO), isopropyl myristate, ethyl butyrate, isopropyl palmitate
Mineral oil	Liquid paraffin
Vitamins	Vitamin E/α-tocopherol
Diethylene glycol monoethyl ether	Transcutol HP
Natural oils	
Fixed oils	Sunflower oil, shark liver oil, palm oil, sesame oil, olive oil, rice bran oil, margosa oil, mustard oil, jojoba oil, cod liver oil, cottonseed oil, arachis/ peanut oil, castor oil, soyabean oil, chaulmoogra oil
Essential oils	Pumpkin seed oil, lemon grass oil, cinnamon oil, peppermint oil, citronella oil, lavender oil, clove oil, garlic oil, geranium oil

Table 3: Surfactants, co-surfactants, and surface modifiers used in the formulation of NLCs [Shamama Javed *et al*,2022].

Agents	Examples
Surfactants/co-surfactants	Soy lecithin (Lipoid S 75, Lipoid S 100), phosphatidyl choline 95% (Epikuron 200), Poloxamer-188 (Pluronic F-68), egg lecithin (Lipoid E 80), Cremophor EL, Poloxamer 407, lecithin, Poloxamine 908, Solutol HS 15, Tyloxapol, Polysorbate 20 (Tween® 20), Polysorbate 60 (Tween® 60), Polysorbate 80 (Tween® 80), sodium cholate, taurodeoxycholic acid sodium, sodium glycocholate, butyric acid and butanol, sodium dodecyl sulfate, cetylpyridinium chloride, polyvinyl alcohol, and sodium oleate
Surface modifiers	Folate, PEG 2000, biotin, ferritin, transferrin, β-D-galactosides, mannose, L-arginine, oligo-chitosan, hyaluronic acid, wheat germ agglutinin

Preparation methods for NLCs

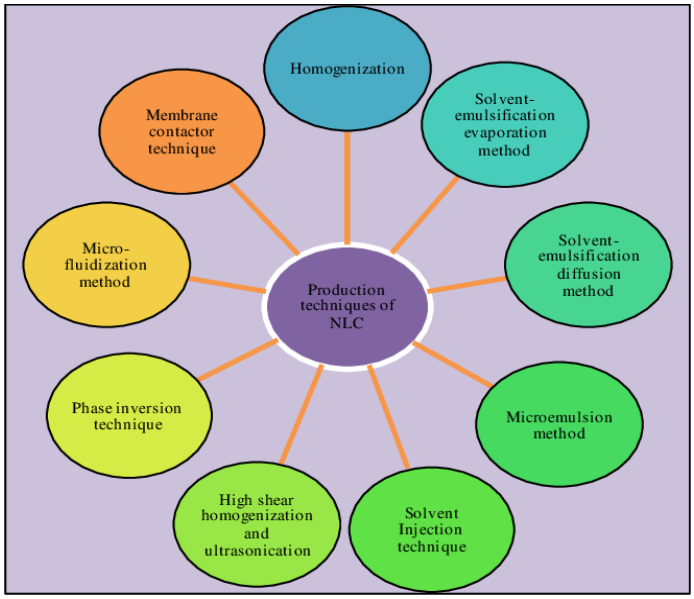

Figure 4. Production Techniques of nanostructured lipid carriers [Neha Kanojia *et al*,2022].

High-pressure homogenizer

The method that produces NLC most frequently is this one. Its advantages over other procedures include the ability to produce on a big scale and the lack of the need for organic solvents. Both the heat homogenization technique and the cold homogenization technique can be used. The initial stage in both approaches comprises dissolving the medication in a melted lipid mixture (LM) (solid+liquid) at a temperature that is 5–10 °C above the lipid melting point

In the **hot homogenization procedure**, the aforementioned melt is stirred into an emulsion in a hot aqueous surfactant solution in order to create a hot nano-emulsion. NLC was then further cooled to room temperature. **In the cold homogenization process,** The melt from step one above was consolidated and crushed to produce lipid microparticles using the cold homogenization process. These were homogenized at reduced/RT to obtain NLC and dispersed in a cold aqueous surfactant solution to obtain presuspension. Hydrophilic medications benefit from this approach [Natarajan J *et al*,2017].

Solvent emulsification/evaporation technique

The lipid phase is dissolved in an organic solvent, such as acetone, in this procedure (organic phase). The organic phase is then continuously stirred at 70–80 °C while being added to the aqueous phase (surfactant solution in water). The stirring will keep going until all of the organic phases have evaporated. In order to harden the lipid nanoparticles, the resultant nanoemulsion is then frozen (below 5 °C). [Parisa Ghasemiyeh *et al*,2018]

Solvent-emulsification diffusion technique.

In this method, the lipids and drug are dissolved in a water-saturated solvent, which is then emulsified in a solution of emulsifier in a solvent-saturated water phase using a homogenizer to create an o/w emulsion. This o/w emulsion is then further diluted with an excess of the aqueous phase, which causes organic solvent diffusion from emulsion droplets to the aqueous phase Ultrafiltration or freeze-drying may be used to remove the solvent. The utilized solvents have a greater safety profile, making solvent diffusion a generally favored adaptable technology. [Neha Kanojia *et al*,2022]

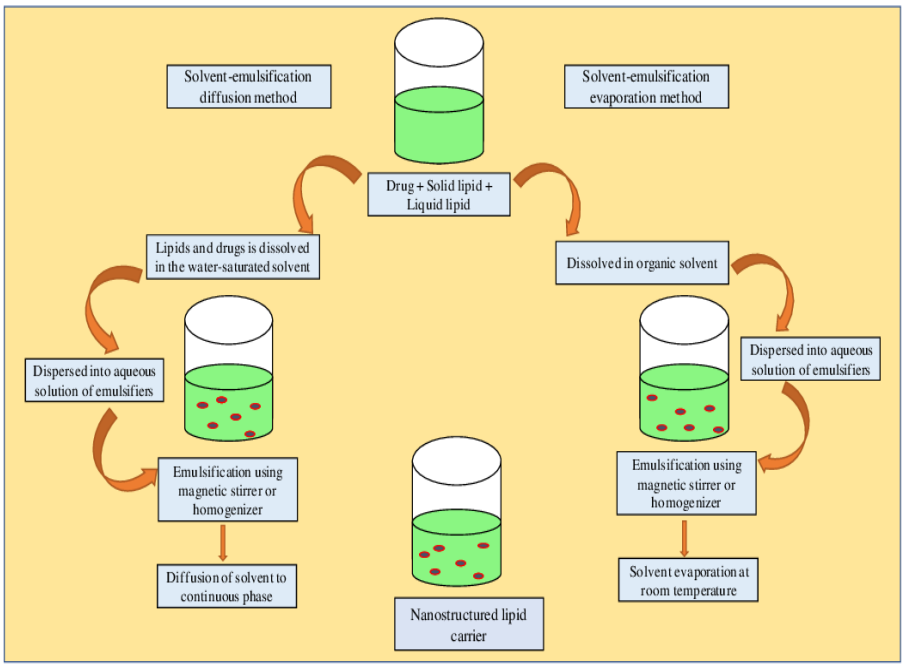

Figure 5. solvent-emulsification and solvent-diffusion evaporation techniques utilized for the production of nanostructured lipid carriers [Neha Kanojia *et al*,2022].

Microemulsion technique

Liquidized lipids (fatty acids or glycosides, such as lipid acids) are then combined with medication. The surface-active agent, co-surfactant(s), and water are all heated to a similar temperature before the lipids are added and gently stirred to soften the lipids. Once the components are combined in the proper ratios for microemulsion production, a transparent, thermodynamically stable system is produced. The microemulsion serves as the starting point for the development of nanoparticles that are the required size. This microemulsion is then dispersed over a very cold liquid medium while a delicate mechanical mixing process gently combines hot microemulsion with water at a ratio of 1:25-2:50. The oil droplets quickly recrystallize as a result of this dispersion in the cool liquid medium [Anonymous,2016].

High Shear Homogenization or Ultrasonication Technique

Both solid and liquid lipids that had been melted received the drug. The temperature of the lipid phase and the water phase are both heated to the same level. Using a probe sonicator, an emulsion was produced and ultrasonically processed. The manufacturing temperature is maintained at least 5 to 10^0C above the lipid melting point to prevent recrystallization throughout the procedure. The emulsion must travel through a 0.45-m membrane in order to be purified [Deepak Patil *et al*,2019].

Supercritical fluid technique

By adding an appropriate surfactant, the medication and lipid material are solubilized in an organic solvent, such as chloroform, and a solution of organic matter is produced. An O/W emulsion is created by distributing the organic solution throughout the aqueous phase, which may or may not also contain a co-surfactant. The O/W emulsion is injected from one end of the extraction column, usually the top, at a constant flow rate, and the supercritical fluid, which is maintained at a constant temperature and pressure, is added at a constant flow rate counter currently. To create LNP dispersions, a continuous solvent extraction process from O/W emulsions is used [Shamama Javed *et al*, 2022].

Solvent injection (or solvent displacement) technique

The technique makes use of dimethyl sulfoxide and ethanol, two solvents that disperse quickly in water. The lipid is first dissolved in the solvent before being swiftly injected with an injection needle into an aqueous solution of surfactants. The lipid particles precipitate in the aqueous solution whereas the solvent migrates quickly in the water. Smaller particles are produced at higher velocities. Larger particles are produced by more lipophilic solvents, which could be problematic. This approach has benefits including low temperatures, low shear stress, easy handling, and a quick production process without the need for technologically advanced equipment (e.g., high-pressure homogenizer). However, the usage of organic solvents is the principal drawback [Amandeep *et al*,2020].

IV. DRUG DELIVERY BY NLCs

NLCs are applicable to a wide range of drug administration techniques, including oral, transdermal, intravenous, and gene transfection [Qianwen Li *et al*,2017].

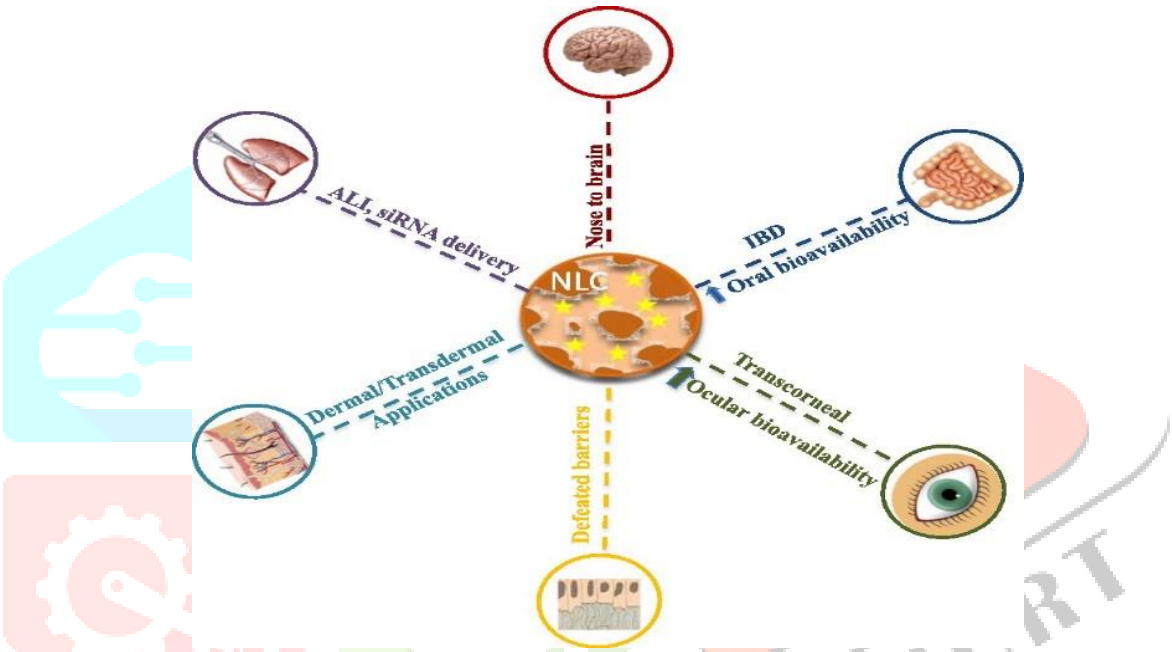

Figure 6. Drug delivery by NLCs [Ana Beloqui *et al*,2016]

NLCs as drug carriers for oral administration

The most popular method for administering medications is oral since it provides a beneficial choice for treating a variety of fatal diseases and has a number of benefits such as patient compliance, cost-effectiveness, and convenience of administration. It is also a top choice for medications that are used on a constant schedule, such as anti-diabetic, anti-tumor, and hypertension medications. The association between improved absorption and the kinds of lipid utilized in the formulation has been the subject of rigorous research by Charman and his colleagues. In order to prepare NLC for oral distribution, a multitude of medications was utilized. Increasing GI absorption or avoiding the drug's first-pass metabolism were the main methods used in most situations to boost oral bioavailability. Although oral drug delivery systems account for a large portion of the market for drug delivery, these systems are constantly looking for better alternatives because of inconvenient factors like poor drug solubility, a narrow window of absorption, rapid metabolism, high variability in drug plasma levels, and variability caused by food effects. These elements could provide unsatisfactory in vivo outcomes that result in the oral administration systems failing. In recent years, a number of the aforementioned issues have been resolved by colloidal drug carriers such micelles, liposomes, neosomes, nanoemulsions, nanosuspensions, and polymeric nanoparticles. However, these systems also have a number of drawbacks, including poor physical stability, buildup, low yield, drug leakage while being stored, the presence of organic solvent residues, cytotoxicity, etc [Rajshri Dusane *et al*,2019]

Drug delivery to the brain

Targeting the brain not only improves the drug's concentration in the cerebrospinal fluid but also lowers the frequency of dose and adverse effects. In comparison to oral administration, the main benefits of this method of administration include avoiding first-pass metabolism and a quick commencement of effect. Because of their quick absorption by the brain, acceptability, and biodegradability, LNC (for example, NLC) of this generation is regarded as one of the major strategies for drug administration without any alteration to the drug molecule. They are more promising carriers for drug delivery because of their scale-up viability and lack of the burst effect. Additionally, NLC improved the intranasal medication delivery of duloxetine for the treatment of the major depressive disorder. To increase the bioavailability and absorption of asenapine maleate into the brain, researchers have developed nanostructured lipid carriers (NLCs). According to in-vivo data, bromocriptine-loaded NLCs have a quicker onset of action, a longer duration, and greater brain levels than those of solution. Entrapment efficiency was also improved [Sarabjot kaur *et al*,2015]

Pulmonary Drug Delivery

Drug Delivery Through Inhalation is a prospective method of administration for the treatment of several respiratory diseases. Compared to polymeric nanoparticles, liposomes, and emulsions, NLCs are more stable against the shear forces produced during nebulization. NLCs enable the high payload of lipophilic medicine since they are made up of an inner oil core encircled by an exterior solid shell. Since the lung epithelium may be directly addressed, NLCs in the treatment of pulmonary illnesses appear to be a promising technique. This allows for a faster beginning of the action, a reduction in the amount of time between doses, and the avoidance of unfavorable side effects. Due to their tiny particle size and lipophilic nature, NLCs' bioadhesive characteristics result in a prolonged residence duration in the lungs [Anonymous,2017].

Ocular application

Due to its unique anatomical structure, the eye is a strongly protected organ and presents a challenge to medication delivery methods. Strong blood-ocular barriers, muco-aqueous barriers, lymphatic tear turnover, the non-pigmented layer of the ciliary epithelium, nasolacrimal drainage (more than 75% of solutions are drained through the nasolacrimal duct), and reflex blinking are just a few of the challenges that hinder ocular bioavailability. Ocular DDS aims to reduce systemic absorption and hence generalized negative effects in addition to improving ocular medication absorption. Lipid nanoparticles have been shown to increase the effectiveness of ocular administration by increasing the penetration of actives through the cornea.

In general, there are several ways that NLCs can get beyond ocular barriers:

- prolongation of drug release and, consequently, of the encapsulated drug's residence duration.
- Transcellular and paracellular processes that increase the drug's bioavailability in the eye.
- overcoming obstacles in the blood-eyes.
- protection from lacrimal enzyme inactivation of the medications that are encapsulated.
- enhancing patient compliance by a reduction in dose frequency [Mohammed Elmowafy *et al*,2021]

Intranasal drug delivery

Due to quick absorption and beginning of an action, avoidance of labile drug (peptides and protein) breakdown in the GI tract, and inadequate transport through epithelial cell layers, nasal administration is a viable alternative noninvasive method of drug delivery. A greater drug concentration in the brain following intranasal delivery was demonstrated by the creation of a stable NLC system as a carrier of curcumin biodistribution. NLC also improved the intranasal medication administration of duloxetine for the treatment of major depressive disorder in the brain. Asenapine maleate NLCs demonstrated increased bioavailability and increased absorption into the brain [N. Y. Nandvikar *et al*,2019].

Parenteral administration

Parenteral drug delivery has been improved by nanomedicine and nanotechnology. The ability to scale up production easily, the biocompatibility and biodegradability of the formulation ingredients, the controlled and modified drug release pattern, the prevention of drug degradation, and the maintenance of more constant serum levels of drugs are the most significant benefits of lipid nanoparticles for this application. Target organs can receive intravenous, subcutaneous, intramuscular, or direct injections of drug-loaded lipid nanoparticles [Parisa Ghasemiyeh *et al*,2018].

Gene transfer

Because lipids are the most crucial elements of cell membranes, LNPs effectively pass through biological membranes via receptor-mediated pathways. increase the absorption of genetic molecules in this way. Particle size has a direct impact on how some bioactive are transported to specific locations in the body and how they behave when released. The development of new bioactive delivery mechanisms is essential for the success of gene therapy (including DNA and RNA transfer). Since 1980, there have been reported findings from more than 400 clinical gene therapy research. Due to bare DNA's limited capacity to transfer to cells and susceptibility to enzymatic destruction, delivery vectors are utilized in gene transfer. Interesting and suitable nonviral gene delivery vectors for systemic distribution are cationic SLNs. For gene transfection, SLNs can bind to DNA directly. Genospheres (like cationic SLNs) hold great promise for the delivery of specific genes. In general, components like plasmid DNA, DNA, and other nucleic acids are carried by genomespheres. They have three crucial characteristics: cationic SLN composition, DNA condensation capacity, and nucleic acid transport to cells. An innovative nonviral gene transfer vector that offers a promising method for gene therapy is NLCs [Neda Naseri *et al*,2015].

V. BENEFITS OF NCLs

- ✓ Better physical stability.
- ✓ Ease of preparation and scale-up.
- ✓ Increased dispersibility in an aqueous medium.
- ✓ High entrapment of lipophilic drugs and hydrophilic drugs.
- ✓ Controlled particle size.
- ✓ An advanced and efficient carrier system in particular for lipophilic substances.
- ✓ Increase of skin occlusion.
- ✓ Extended release of the drug.
- ✓ One of the carriers of choice for topically applied drugs because their lipid components have an approved status or are excipients used in commercially available topical cosmetic or pharmaceutical preparations.
- ✓ Small size of the lipid particles ensures close contact with the stratum corneum thus enhancing drug penetration into the mucosa or skin.
- ✓ Improve benefit/risk ratio.
- ✓ Increase skin hydration and elasticity.
- ✓ These carriers are highly efficient systems due to their solid lipid matrices, which are also generally recognized as safe or have a regulatory accepted status [Chandana karnati *et al*.2019, Ana Beloqui *et al*.2016, Piyush Jaiswal *et al*.2014].

VI. LIMITATIONS OF NLCs

- ➢ Cytotoxic effects are observed because of the nature of the matrix and concentration.
- ➢ Some surfactants exhibit irritative and sensitizing actions.
- ➢ Clinical and preclinical studies lacked in the preparation of NLCs.
- ➢ Application and efficiency in the case of protein and peptide drugs and gene delivery systems still need to be better exploited. [Chandana karnati *et al*.2019, Amandeep *et al*.2019, Piyush Jaiswal *et al*.2016].

VII. PARAMETERS FOR EVALUATION

Particle size

The physical stability of the vesicle dispersion depends on particle size, and as particle size falls, surface area characteristics rise as a function of total volume, making particle size a crucial component in process control and quality assurance. An effective approach for research that may be used with particles from 200 nm in size up to 1μm is photon correlation spectroscopy, which is based on the diffraction of laser light [N. Y. Nandvikar *et al*,2019].

Zeta Potential

The assessment of the dispersion and aggregation processes impacting particle stability in the application is done by the measurement of surface charge. Due to electrostatic repulsion, charged particles generally have a lower likelihood of aggregating or fusing together. Due to binding to the paracellular region of the BBB, which is a region rich in anionic sites, NLCs with a positively charged surface is effective in crossing the blood-brain barrier (BBB). To determine if the desired cationic surface has been created, the zeta potential measurement is useful for formulation design. To stabilize the nanoparticulate systems during storage, a particulate surface may occasionally need to be negatively charged [Chia-Lang Fanga *et al* ,2013]

Atomic Force Microscopy

AFM micrographs were obtained to evaluate the morphological changes and the particle size of NLCs before and after lyophilization. Atomic force microscopy (AFM) observation was carried out using a Nano surf mobile (nanosurfe ag, liestal, switzerland). The pictures were produced by measuring the forces that interacted with the sample surface at the tip. The studies were conducted in a non-contact mode in the air at an ambient temperature (250 c). On a tiny mica disc, suspension droplets were arranged in droplets. The measurements were made at several sample sites. The amplitude AFM images were captured prior to and during the freeze-drying of NLCs under ideal conditions. i.e., a freezing temperature of -700 c applied at a time period of 24 h, and a sublimation time of 48 h. Image data were analyzed with easy scan 2 software [Anonymous,2017].

Dynamic Light Scattering (DLS)

Dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS), is a valuable tool for measuring diameters ranging from a few nanometers to three micrometers. It analyses the variation in the intensity of the scattered light produced by particle movement (diffusion). However, it is advised to use laser diffraction (LD), often referred to as static light scattering, to quantify particles in the SLN and NLC formulations that have sizes higher than 3 μm. Smaller particles produce more intense scattering at high angles than bigger ones do (Fraunhofer spectra), which is related to the diffraction angle on the particle radius. If the particles are not spherical, it is always best to use both the PCS and LD procedures at the same time [Hamdi Nsairat *et al*,2021].

Differential Scanning Calorimetry

Differential scanning by measuring the glass and melting point temperatures at their respective enthalpies, calorimetry is utilized to ascertain the speciation of crystallinity and polymorphism of bulk materials, medications, and medication nanoparticles [Anonymous,2013] Differential Scanning Calorimeter (822e, mettler Toledo, greifensee, switzerland). In pinhole-bottom sealed aluminum pans with lids, 10 mg of bulk lipid, medication, and lyophilized NLC were heated. The reference object was an empty metal pan. With a continuous linear heating rate of 5°C per minute in pure ultrahigh dry nitrogen, differential scanning calorimetric curves were acquired from 20°C to 80°C. Values are provided as the average of three determinations after three iterations of the study. Lastly, the Mettler star program was used to determine the enthalpies [S. Mukherjee *et al*,2009]

Degree of Crystallinity

The encapsulation effectiveness and release rate of medicinal drugs from NLCs are strongly influenced by the crystal lattice's structure and the condition of its lipid constituents. The encapsulation of pharmaceuticals benefits, in theory, from greater crystal lattice flaws. Varying lipids have different melting enthalpies and melting points, hence differential scanning calorimetry may be used to assess the condition of the lipid components. The quantity of medication loaded, storage period, and formulation viscosity can all have a substantial impact on the crystallinity of lipid-based NPs. Due to the drug's improved entrapment and housing in the lipid matrix, employing SL with a variety of crystal lattice defects can boost both the drug's encapsulation and chemical stability in NLCs [Mohamed Haider *et al*,2020].

Scanning electron microscopy (SEM)

Scanning electron microscopes were used to analyze shape and surface morphology. The NLCs powder was sparingly sprinkled over an adhesive tape that was adhered to an aluminum stub to create the samples for SEM. The stubs were then coated with gold using a sputter coater to a thickness of roughly 300. A 20kV scanning electron microscope was used to examine each sample, and appropriate magnifications were used to acquire photomicrographs [Amrendra Yadav *et al*,2021].

Entrapment efficiency

Entrapment efficiency estimates the amount of medication that is trapped inside NLCs, reflecting the effectiveness of the nanosystem in doing so. Due to the characteristics of NLCs (high lipid content), which delay the leaking of the entrapped drug, high entrapment efficiency of lipophilic medicines has been found. This is because the drug is homogeneously dissolved inside the lipid. Equation (1) can be used to determine the quantity of drug trapped in NLCs and measure it spectrophotometrically at the appropriate max after adding enough organic solvent (such as methanol) to dissolve the NLCs and release the drug. [Eman Gomaa *et al*,2021]

$$\textbf{Entrapment efficiency (\%)} = \frac{\text{Amount of entrapped drug}}{\text{Total amount of initially added drug}} \times 100$$

The amount of free medication in the supernatant after centrifuging the loaded NLCs suspension can also be determined indirectly using equation (2) by taking spectrophotometric measurements at the relevant λmax.

$$\textbf{Entrapment efficiency (\%)} = \frac{\text{Total amount of initially added drug} - \text{Unentrapped drug}}{\text{Total amount of initially added drug} \times 100} \times 100$$

Drug release

The medication release investigation was conducted using the dialysis bag technique. The dialysis tube (10 kDa molecular cut-off) was carefully prepared according to the protocol (Sigma) the day before the drug release experiment and left in the release media overnight. As a drug release medium, phosphate buffer (10 mM, pH 7.4) with 2% Tween 80 was utilized. The dialysis tube was filled with a precisely measured 1 mL of formulation, and both ends were securely secured to stop any leaks. The 10 mL of release media-filled glass container with 10 mL of amber hue was then used to store the tube holding the formulation. The bottle was maintained on a horizontal, 100-rpm spinning shaker made by Sartorius in Germany. At the preset intervals, samples (5 mL release media) were taken out of the bottle and replaced with 5 mL brand-new release media. The amount of medicine released from the formulation at various times was then calculated from the samples using HPLC analysis. The tests were carried out three times [Mohamed Haider *et al*,2020].

VIII. NANOSTRUCTURES FOR THE TREATMENT OF BRAIN DISEASE

It has been exceedingly difficult to synthesize nanoparticles for the treatment of brain illnesses. In order to create a delivery system with certain properties like high loading efficiency, biocompatibility, and stealth qualities, a variety of delivery techniques have been used. However, the BBB crossing property is the most crucial property. Lipid-based nanostructures like liposomes, SLNs, NLCs, lipoplexes, lipoproteins, polymeric nanoparticles, polymeric micelles, dendrimers, and inorganic nanoparticles like iron oxide, ceria, gold, and quantum dots are among the most significant nanostructures that have been studied for the delivery of therapeutics in the CNS [Christos Tapeinos *et al*,2017].

NLCs in brain cancer

As a result of their high biocompatibility and minimal immunogenicity, NLCs are regarded as the finest prospects for treating CNS illnesses. Due to their desirable characteristics, NLCs have been employed to treat a variety of brain conditions, but mostly brain cancer. In a number of studies, SLNs and NLCs were described as effective nanocarriers with exceptional qualities that could increase the therapeutic efficacy of anti-cancer drugs used to treat brain tumours. Additionally, brain tumours have a large buildup of SLNs and NLCs, which facilitate anticancer drugs' easy passage through the BBB. In order to successfully target a brain tumour, NLCs are advantageous lipid nanocarriers. Studies on the efficiency of ferulic acid-laden NLC against the U87MG glioblastoma cancer cell line as well as loaded NLCs adorned with didodecyldimethylammonium bromide to compare the anticancer effectiveness with uncoated NLC were undertaken. Results demonstrated that the NLC was more effective than the uncoated free medication [Hamdi Nsairat *et al*,2021].

Table 4 : Basic properties and characteristics of NLCs used for the treatment of brain Cancer

Type of Carrier	Solid Lipid	Liquid Lipid	Emulsifiers/ Stabilizers/ Surfactants	Preparation Method	T (∘C)	Size (nm)	Zeta (Mv)	EE (%)	DL (%)	Therapeutic Molecule	Targeting Moiety	In-Vitro	In-Vivo
NLC	compritol® 888ATO,SPC	Soya lecithin	Cremophor®ELP, Tween® 80 & DDAB	SDM	80 - 85	121.4 ± 5.6	+29.1 ± 2.4	81.4 ± 3.7	5.2 ± 0.6	TMZ	N/A	U87MG	BALB/c nude mice(5-6 week – old, 18-22 g)
NLC	precirol®ATO5	Oleic Acid	Tween® 80	EUT	75	105.4 ± 2.5	-21.6± 3.1	84.62± 4.98	15.31±3.29(ug/mg)	CRB	N/A	Leukemic EL-4	N/A
NLC	StA	Oleic Acid	Tween® 80	EUT	80	90.7± 4.28	-24.2 ±1.89	49.5 ± 2.24	N/A	CRB	N/A	Leukemic EL - 4	N/A
NLC	CP, Stearylamine or Dodecylamine or Spermine	Octyl Dodecalnol, Soy Lecithin	Poloxamer 188	SDM & EUT	60	125 to 247	+25 to +45	19 to 90	0.39 to 1.86	ETP	Trf	K562	N/A
NLC	Precirol® ATO	Capmul®, Soya Lecithin	Tween® 80	HPH	85	146.8	21.4 ± 1.87	90.86	N/A	CUR	N/A	U373MG	Male Wistar rats (250 – 270 g)

Table 4: Basic properties and characteristics of NLCs used for the treatment of brain cancer

NLC	Compritol® 888 ATO, and SPC RGD-PEG-DSPE	Soya lecithin	Cremophor® ELP, Tween 80 &DDAB	SDM	80-85	179	±23	83	GL:91 %	TMZ & DNA	RGD	U87MG	BALB/c Nude mice (5-6 week-old, 18-22 g)
NLC	Compritol® 888 ATO, SPC	Soya lecithin	Cremophor® ELP & DDAB	SDM	70-75	With RGD 118.3±2.6 w/o RGD 93.6 ± 2.1	With RGD ±28.9±2.9 w/o RGD ±23.3 ± 2.7	With RGD 84.7±3.2 w/o RGD 85.3 ± 2.3	With RGD 5.6±0.5 w/o RGD 7.3 ± 0.9	TMZ	RGD	U87MG	BALB/c Nude mice (5-6 week-old, 18-22 g)
NLC	Compritol® 888 ATO, SPC	Soya lecithin	Cremophor® ELP & DDAB	SDM	70-75	117.4±2.8	+29.8+3.2	VCR:85.4 ±2.8 TMZ: 88.9 ± 3.6	VCR:5.7 ±0.5 TMZ: 6.8 ± 0.7	TMZ & VCR	N/A	U87MG	BALB/c Nude mice (5-6 week-old, 18-22 g)
NLC	Tripalmitin	Oleic Acid	Tween® 80	HSHT, HPH	70	214	N/A	88.6	27.4	CUR	N/A	A172	Female nude mice, 5-6 weeks-old,A172 xenograft
NLC	Cholesterol, Triolein, Stearylamine	Soya lecithin	Poloxamer 188	SEEM	45	205.4±11	25.7±6.22	91.8±0.5	5.38±0.03	PTX	Trf	U87MG	N/A

NLCs in ischemic stroke

SLNs and NLCs have been used in very few therapeutic approaches described in the literature during the past seven years, despite the fact that ischemic stroke has one of the highest rates of morbidity and mortality in the world. One of the causes might be the utilisation of related polymeric systems, which have the benefit of more adaptable surface functionalization as compared to lipid nanostructures.

One of the seven-year-old trials employed vinpocetine (VIN), a lipophilic medication used to treat chronic cerebral vascular ischemia. Its limited bioavailability and brief half-life are caused by its lipophilic nature. In order to get around these restrictions, VIN loaded NLCs (VIN-NLCs) with sizes ranging from 100 to 200 nm, a charge that is slightly negative, and an encapsulation efficiency of roughly 95% were created. The study's findings showed a continuous release profile without any burst releases as well as a 322% improvement in bioavailability over the free medication. A few years following the completion of this trial, VIN's improved therapeutic efficacy was reported in two more scientific papers. In the first investigation, various SLN formulations were created using the high shear/speed homogenization technique (HSHT), with the goal of identifying the formulation that would best facilitate the loading and release of VIN. The results of the best formulation indicated its potential application as a controlled delivery system, with an encapsulation efficiency of more than 83% and a sustained release profile for over 96 h. A different method for fabricating VIN-NLCs was used in the second investigation.

In this study, the authors created NLCs using Compritol® ATO 888 that contained complexes of vinpocetine, cyclodextrin, and tartaric acid (TA). The in vivo tests conducted on New Zealand rabbits showed improved oral bioavailability of 92% compared to VINNLC and 522% compared to free VIN. Three years later, a focused strategy utilising baicalin contained in NLCs was presented. Additionally, it was demonstrated that baicalin had a better bioavailability in the cerebral spinal fluid of rats with cerebral ischemia-reperfusion injury as well as increased brain uptake [Christos Tapeinos *et al*,2017].

Table 5 - Basic properties and characteristics of NLCs used for the treatment of ischemic stroke

Type of carrier	Solid lipid	Liquid Lipid	Emulsifiers/ stabilizers/ surfactant	Preparation method	T (°C)	Size (nm)	Zeta (mV)	EE (%)	DL (%)	Therapeutic molecule	Targeting moiety	In Vitro	In vivo	Year
NLC	Compritol® ATO 888, GMS	Miglyol® 812N, Lecithin	Solutol® HS15, Poloxamer 188	HPH	85	107-177	13 to -25	94.9 ±0.4	1.80± 0.12	VIN	N/A	N/A	Male Wistar rats (200−250 g)	2010
NLC	Compritol® ATO 888	Miglyol® 812N	Solutol® HS15	EUT	85	89-148	-12 to +13	59-86	N/A	VIN	N/A	N/A	New Zealand white male rabbits, (2.5±0.2 kg)	2014
NLC	Tripalmitin, Gelucire®, SPC, Vitamin-E	-	Poloxamer 188	EUT	80	93-102	50 to -57	91-94	N/A	Baicalin	N/A	N/A	Male Wistar albino rats (200−250 g)	2012

NLCs in Parkinson's disease

Another neurodegenerative condition that causes a gradual movement disorder is Parkinson's disease. Although PD does not directly pose a threat to life, its symptoms drastically lower the quality of life for those who have it. There is currently no effective treatment for Parkinson's disease (PD), but it does have some therapeutic benefits. Over the years, a few trials for the treatment of PD have been reported, some of which included the use of various medications encapsulated in SLNs and NLCs, including apomorphine (APO). A comparison study of the three formulations in which APO was encapsulated—SLNs, NLCs, and lipid emulsions (LEs)—was performed.

Sulforhodamine B (SRB) was used in in vivo real-time bioluminescence tests on the brain of male Sprague-Dawley rats to show that NLCs may aggregate to specific brain regions more readily than the other two formulations.

Ropinirole (RPN) was used as the encapsulated drug inside NLCs once more in a study whose major objective was to investigate the impact of surface charge on the brain when administered orally. The creation of anionic and cationic NLCs with absolute surface charges of 34 mV resulted in the moderate inflammation of the nasal epithelium in the case of the former and the destruction of the mucosal nasal epithelium in the case of the latter. The anionic NLCs also demonstrated the highest drug targeting efficiency, despite the cationic NLCs showing a larger concentration in the brain epithelium. Another form of hybrid lipid nanoparticles that have been reported for the treatment of Parkinson's disease (PD) is gelatin nanostructured lipid carriers (GNLs) [Christos Tapeinos *et al*,2017].

Table 6 - Basic properties and characteristics of NLCs used for the treatment of Parkinson's disease

Type of carrier	Solid lipid	Liquid Lipid	Emulsifiers/ stabilizers/ surfactant	Preparation method	T (° C)	Size (nm)	Zeta (mV)	EE (%)	DL (%)	Therapeutic molecule	Targeting moiety	In Vitro	In vivo
NLC	CP, DSPE-PEG5000	Squalene	Pluronic ® F68, Myverol Forestall, Tween ® 80	HSHT-EUT	85	373 - 430	+42 to +51	59-61.5	N/A	APO, SRB	N/A	N/A	Male Sprague Dawley rats (230–270 g)
NLC	CP	Sesame oil	Pluronic ® F68, Myverol	HSHT-EUT	85	213.5 ±1.5	−20.8 ±2.8	N/A	N/A	DAA, R800	N/A	Erythrocytes	Female nude mice (ICR Foxn1nu strain, eight weeks old)
	CP, DSPE, PEG5000		Pluronic ® F68, Myverol, Forestall			250.1 ±3.3	48.4 ±0.6						
A -NLC	Compritol® 888 ATO, Labrafac™ Lipophile WL1349	-	Pluronic ® F127, Pluronic ® 68, Tween ® 80, Epikuron 200	HSHT	80	82 to 314	-39 to +34	32 to 79	N/A	RPN	N/A	N/A	Male Wister albino rats (200–250 g)
C-NLC	Compritol® 888 ATO, Labrafac™ Lipophile WL1349, Stearylamine												

NLCs in Alzheimer's disease

Alzheimer's disease (Alz) sufferers are unable to manage daily duties due to memory loss and other cognitive impairments. Depending on the patient, the disease progresses in different ways, but it always results in death after a typical life span a three to nine-year life expectancy. We will concentrate on the research that use different lipid nanoparticles in this section because there have been many studies published for treating AD. Huperzine A has been one of the medications used to treat AD (HupA). HupA is a cholinergic that functions as a cognitive transmitter and may benefit people with AD. In the past seven years, two studies have been presented that used SLNs and NLCs to contain encapsulated HupA.

the authors prepared CP-based NLCs loaded with HupA, and they studied their morphological characteristics as well as their physicochemical properties. The size of the NLCs was 120 nm and their surface charge was -22.93 mV. The NLCs presented a good loading efficiency (89.18%), although their loading capacity was not so high (1.46%). The in vitro release profiles showed a controlled drug release for up to 96 h [Christos Tapeinos *et al*,2017].

Table 7 - Basic properties and characteristics of NLCs used for the treatment of Alzheimer's disease

Type of carrier	Solid lipid	Liquid Lipid	Emulsifiers/ stabilizers/ surfactant	Preparation method	T (°C)	Size (nm)	Zeta (mV)	EE (%)	DL (%)	Therapeutic molecule	Targeting moiety	In Vitro	In vivo
NLC	CP	Miglyol® 812	Soybean phosphatidylcholine, Solutol® HS15	EUT-HPH	52	120	-22.93 ±0.91	89.18 ±0.28	1.46 ±0.05	HupA	N/A	N/A	N/A
NLC	GMS	Capmul® MCM	Transcutol ® P, Tween ® 80	MEM	60-63	137.1 ± 10.4	– 17.5 ± 7.16	99.38 ± 1.08	N/A	HupA	N/A	N/A	Male Swiss Albino mice (25–30 g, 4–6 weeks old)
NLC	PC, Cholesterol oleate	Glycerol triolate	-	SEvaM	40	75-163	-3.5 to -17	87-97	2.60 ± 0.17	CUR	Lf	BCEC	Sprague Dawley rats (180–220g) and ICR mice (18–22g)

NLCs in for treating other diseases of the CNS.

The main CNS illnesses that have been treated using NLCs formulations over the past seven years include: Despite the fact that numerous journals that covered numerous. Despite the fact that the CNS diseases have been discussed, numerous scientific investigations are still ongoing regarding more CNS diseases. We won't go into great depth about these studies because the main focus of our review is on the use of and NLCs for the treatment of the major CNS illnesses. NLCs for the treatment of the main CNS diseases. Hodgkins disease, schizophrenia, epilepsy &bipolar disorder behavioral disorder, migrane [Christos Tapeinos *et al*,201

Table 8 - Basic properties and characteristics of SLNs & NLCs used for the treatment of various diseases of the CNS.

Type of carrier	Solid lipid	Liquid Lipid	Emulsifiers/ stabilizers/ surfactant	Preparation method	T (°C)	Size (nm)	Zeta (mV)	EE (%)	DL (%)	Therapeutic molecule	Target	Targeting moiety	In Vitro	In vivo
NLC	GMS	Oleic acid	Tween ® 80	HSHT, EUT	70	167.3 ±7.52	-4.33± 1.27	83.50±2.48	N/A	ASN	Schizophrenia	N/A	N/A	Male Charles Foster rats (200–240 g)
NLC	GMS	capryol PGMC	Pluronic ® F68, (sodium tauracholate	HSHT, EUT	N/A	137.2 ±2.88	31.53 ±11.21	79.15±4.17	9.73 ±3.22	DLX	Behavioral disorders	N/A	N/A	Swiss albino Wistar rats of either sex (150-250 g)
NLC	Crodamol SS®, Crodamol GTCC®, SPC, DSPEPEG2000-MAL	Soya lecithin	Solutol ® HS15	EUT	70	96.46 ±0.15	0.78± 0.35	93.11±2.67	N/A	TXL	Brain cancer	Pcpp	HT-1080	N/A

NLC	Stearyl amine, Precirol ® ATO5, GB	Kolliphor® P188, MCT	Vitamin-E, Soybean lecithin	HSHT	5 °C above melting point	190± 10	43.5± 1.2	98.5	14	DCB	Brain cancer & Hodgkin's disease	N/A	N/A	N/A
NLC	CP	Soy lecithin, octyl-dodecanol	Poloxamer 188	SDT-EUT	50	154± 16	−10± 0.5	N/A	47± 0.8	VPA	Bipolar disorder, Migraines	N/A	N/A	Male Wistar rats (180–210 g)
NLC	GMS, SA, MCT	Soya lecithin	Vitamin-E	SEvaM	70	215.2	−20.1 ±1.22	89.95±0.16	3.05 ±0.01	QRT	Antioxidant	N/A	N/A	Male Kunming mice (20 ± 2 g)
NLC	GMS	Oleic Acid	Poloxamer 407	SIT	58	180 to 271	-39.8 to -22.34	>90	N/A	SMV	Ischemia	N/A	N/A	Balb/c mice (25–30g)
NLC	Witepsol ® H 175	Capmul ® MCM	Tego Care 450	EUT	~45	162-324	-25.94 to -49.2	65-89	N/A	IDB, ILO	Schizophrenia	N/A	N/A	Wistar rats (200–250 g)
NLC	Compritol ® 888 ATO, CP, Precirol ® ATO5, PEG-8	Labrafac CC, almond oil, castor oil, olive oil, oleic acid	Tween ® 80, Poloxamer 188	EUT	70	151.6 ±7.6	11.75 ± 2.96	96.64±4.27	N/A	LMT	Epilepsy & bipolar disorder	N/A	N/A	Ex vivo-Goat nasal mucosa In vivo-Male Wistar rats (150 -- 200 g)

IX. RECENT PATENTS ON NANOSTRUCTURED LIPID CARRIERS [Neha Kanojia *et al*,2022]

The utilisation of non-toxic, biodegradable, and biocompatible excipients such lipids and emulsifiers, as well as reduced regulatory obstacles, are key factors in NLC's rising popularity and global accomplishments. All of the components utilised have received approval from regulatory authorities to encapsulate active chemicals in pharmaceutical and food products, or they are generally recognised as safe. Most are obtained or consist of naturally occurring substances found in the human body, like fatty acids and glycerol. These are well tolerated and have a reputation for reducing cytotoxic or negative drug responses. Over the past few years, lipid nanostructure carriers have been used to examine a variety of medicinal substances.

Table 9 - Patents on Nanostructured Lipid Carriers

Patent name	Patent number	Applicant	Publication date
Nanostructured liposome vector with highly effective antineoplastic activity	CN101011358	Zhejiang University	08.08.2007
Silybin nanostructured lipid carrier and preparation method thereof	CN101632638	Shandong University	27.01.2010
Coenzyme Q nanostructured lipid carrier and preparation method thereof	CN101658468	Suzhou Nanohealth Biotech Co., Ltd.	03.03.2010
zithromycin nanostructured lipid carrier and preparation method thereof	CN101658493	Suzhou Nanohealth Biotech Ltd.	03.03.2010
Nanostructured lipid carrier, preparation method, and application thereof	CN101890170	Shanghai University of T.C.M.	24.11.2010
Method for preparing a nanostructured lipid carrier and a product manufactured by the same	KR1020110137263	Malaysian palm oil board	22.12.2011
Nanostructured lipid carrier (NLC) drug delivery systems for treatment of neurodegenerative disorders	IN1251/MUM/2012	Vikrant T. Kadam	01.06.2012
Resveratrol nanostructured lipid carrier and preparation method thereof	CN102614091	Xia Qiang, Zhao Wujun	01.08.2012
Nanoparticle formulations for skin delivery	US20120195957	Sachdeva Mandip Singh,Florida Agricultural and Mechanical University Patlolla Ram	02.08.2012
Composite anti-screening agent nanostructured lipid carrier and preparation method thereof	CN102688152	Southeast University	26.09.2012
Nanotechnology-based herbal composition for safe and effective treatment of psoriasis	IN422/MUM/2011	Singh Kamalinder Kaur, Patel Medha Chetan	12.07.2013

Thymoquinone loaded nanostructured lipid carriers (tq-nlc) and uses thereof	MYPI 2012001818	Universiti Putra Malaysia	25.10.2013
Nanostructured lipid carrier loaded with phenylethyl resorcinol,preparation method thereof, and cosmetic containing same	CN103860389	Beinong biochemical (Suzhou Industrial Park) Co., Ltd. Suzhou Nanohealth Biotech Co., Ltd.	18.06.2014
Podophyllotoxin preparation resisting condyloma acuminata relapse and HPV latent infection	CN103893167	Nanfang Hospital of southern medical university	02.07.2014
Psoralen-doxorubicin-loaded composite nanostructured lipid carrier preparation and preparation method thereof	CN104367549	Liaoning University	25.02.2015
Idebenone lipid nanocarrier composition for the treatment of neurodegenerative disorders	IN276/MUM/2014.	Sachin Subhash Salunkhe	11.09.2015
Nanostructured Lipidic-polymeric pharmaceutical composition encapsulating drugs	IN2074/DEL/2014	Panjab University	29.01.2016
Nanostructured solid lipid carrier coating vitamin A palmitate and preparation method thereof	CN105496801	Shanghai Institute of Technology	20.04.2016
Hydrophilic modification asiatic acid Nanostructured lipid carrier and preparation method thereof	CN105919976	Zhejiang Academy of Medical Sciences	07.09.2016
ICAM-1 monoclonal antibody-modified simvastatin nanostructured lipid carrier and preparation and application	CN106074389	Zhejiang University	09.11.2016
N-acetyl-L-cysteine modified curcumin Nanostructured lipid carrier used for oral administration	CN106176677	China Pharmaceutical University	27.07.2016
Topical nanodrug formulation	US15163724	Hamidreza Kelidari Majid Saeedi	26.01.2017
A nanostructured lipid carrier encapsulates zingiber officinale oi	MYUI 2015002695	Universiti Teknologi Malaysia	02.05.2017
Nanostructured lipid carrier modified by glycolipid polymer as well as preparation method and application of Nanostructured lipid carrier	CN107115531	Zhejiang University	01.09.2017
A nanostructured lipid carrier encapsulates orthosiphon stamineus extract	MYPI 2016300023	Universiti Teknologi Malaysi	29.06.2018
Cyclic peptide modified gambogic acid Nanostructured	CN108853054	Tianjin University of Traditional Chinese Medicine	29.06.2018

lipid carrier and preparation method thereof			
Polymer thermosensitive liposome loaded with yeast glucan and carnosic acid	CN108904450	Guangzhou Jiayuan Pharmaceutical Technology Co., Ltd.	30.11.2018
Curcumin nanostructured lipid carrier having improved heat stability and efficient stabilization heat treatment method thereof	KR1020190024397	Industry Academy Cooperation Foundation of Sejong University Industry Academy Cooperation Foundation of Sejong University	08.03.2019
Ocular drug delivery	WO/2019/123420	Waterford Institute of Technology	27.06.2019
Nanostructured lipid carrier (NLC) for collaborative treatment of glioma as well as preparation method and application of NLC	CN110013471	Stomatology/Affiliated Stomatology Hospital of Guangzhou Medical University	16.07.2019
A Nanostructured solid lipid carrier encapsulates bromelain extract	MYPI 2018300001	Universiti Teknologi Malaysia	22.07.2019
Novel nanostructured lipid carrier-based ophthalmic controlled release formulation for treatment in fungal keratitis	IN201811021213	Manish Kumar Ajay Pathania Vipin Saini A. Pandurangan Shailendra Bhatt Prerna Sarup	13.12.2019
Nanostructured lipid carriers and stable emulsions and uses thereof	EP3638207	Infectious Disease Res Inst	22.04.2020

X. CONCLUSION

The newest generation of formulations, known as NLCs, allow far greater flexibility in drug loading, regulation of release, and increased performance when manufacturing final dosage forms such injectables, creams, tablets, and capsules. NLC is a promising method for increasing the bioavailability of highly lipophilic medicines with poor water solubility, significant first pass metabolism, affinity for P-gp efflux transporters, and vulnerability to intra-enterocyte metabolism. Comparing NLC to other lipid-based formulations (SLN and LE) with uniform lipid matrices, these carriers can increase the drug distribution to the target organ, alter the pharmacokinetic characteristics of drug carriers to enhance the therapeutic effect, and ultimately enhance drug absorption, and reduce adverse side effects There is still a large need for medicines for incurable diseases including cancer, HIV, ischemic stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, myocardial infarction, atherosclerosis, and others, even though many of the results of these investigations have been marketed. In the biomedical area, nanostructured lipid carriers are becoming more and more popular for the treatment of many illnesses, including brain tumours and neurodegenerative disorders. They are good candidates for the therapy of several CNS illnesses due to their tiny size and innate capacity to cross the BBB, even without any surface functionalization.

ABBREVIATIONS

A172 = Human Brain Cancer Cell Line, AD = Alzheimer's Disease, AFM = Atomic Force Microscopy, APO = Apomorphine, ASN = Asenapine, BBB = Blood-Brain Barrier, BCEC = Brain Capillary Endothelial Cells, CNS = Central Nervous System, CRB = Cytarabine, CUR = Curcumin,DAA = Diacetyl Apomorphine, DCB = Decarbazine, DDAB = Dimethyl Dioctadecyl Ammonium Bromide, DLS = Dynamic Light Scattering,DLX = Duloxetin, ETP = Etoposide, EUT = Emulsification Ultrasonication Technique, GB = Glyceryl Behenate, GMS = Glyceryl Monostearate,GNLS = Gelatin Nanostructured Lipid Carriers, HPH = High Pressure Homogenization, HSHT = High

Speed Homogenization Technique, HT-1080 = Human Fibrosarcoma Cells, HUPA = Huperzine A, IDB = Idebenone, ILO = Iloperidone, LD = Laser Diffraction, Les = Lipid Emulsions, Lf = Lactoferrin, LMT = Lamotrigin, MCT = Medium Chain Triglycerides, MEM = Microemulsion, NLCs- Nanostructured Lipid Carriers, PC = L-Phosphatidyl Choline, PCPP = Photo-Responsive Cell Penetrating Peptide, PCS = Photon Correlation Spectroscopy, PD = Parkinson's Disease, PEG = Poly Ethylene Glycol, PTX = Paclitaxel, QRT = Quercetin, RGD = Arginine-Glycine-Aspartic Acid, RPN = Ropinirole, SDM = Solvent Displacement Method, SDT = Solvent Displacement Technique, SEEM = Solvent Emulsification/Evaporation Method, SEM = Scanning Electron Microscopy, SEVAM = Solvent Evaporation Method, SIT = Solvent Injection Technique, SLNs = Solid Lipid Nanoparticles, SMV = Simvastatin, SPC = Soybean Phosphatidylcholine, SRB = Sulforhodamine B, STA = Stearic Acid, TMZ = Temozolomide, TRF = Transferrin, TXL = Taxol, U87MG = U87 Malignant Glioma Cells, VCR = Vincristine, VIN = Vinpocetine, VPA = Valproic Acid

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