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Review Article

A Comprehensive Review on Nanostructured Lipid Carriers

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Abstract

Nanostructured lipid carriers (NLCs) mark a pivotal evolution in lipid-based drug delivery, surpassing the constraints of solid lipid nanoparticles (SLNs) to optimize therapeutic performance. Formulated with a mix of solid and liquid lipids, NLCs disrupt the rigid crystalline structure of SLNs, facilitating enhanced drug encapsulation, greater stability, and tailored release kinetics for both hydrophobic and hydrophilic compounds. This review thoroughly examines NLCs, detailing their composition, scalable production methods, and assessment techniques. Employing biodegradable lipids and surfactants, NLCs enable environmentally sustainable manufacturing without organic solvents, ensuring biocompatibility and safety. Their adaptability supports a wide range of biomedical uses, such as targeted drug delivery, gene therapy, and vaccine development, enhancing patient adherence and clinical outcomes. The review also explores recent patents and innovative advancements, highlighting NLCs' potential to transform pharmaceutical formulations. Despite obstacles like long-term stability and regulatory challenges, continuous progress in lipid nanotechnology establishes NLCs as a robust platform for next-generation drug carriers. This work illuminates the interplay of stability, functionality, and safety in NLC development, providing insights into their revolutionary impact on modern pharmaceutics and their capacity to meet unaddressed clinical demands.

Keywords: Nanostructured lipid carriers (NLCs), lipid-based drug delivery, targeted drug delivery, gene therapy and vaccine development

1. INTRODUCTION:

Lipid-based Drug Delivery Systems (DDS) are well-established, commercially viable approaches used in the pharmaceutical industry for formulating various dosage forms.[1] Lipid nanoparticles (LNPs) emerged as a significant advancement in the early 1990s with the introduction of the first-generation solid lipid nanoparticles (SLNs).[2] The discovery of solid lipid nanoparticles (SLNs) generated widespread global interest, prompting extensive research into their potential. Over time, SLNs have proven to be a promising alternative to traditional delivery systems such as emulsions, liposomes, and polymeric nanoparticles.[3, 4]

The idea was first introduced by Professor R.H. Müller from Germany and Professor M. Gasco from Italy as an innovative formulation strategy, offering multiple advantages including the utilization of lipids that are compatible to the biological system, reduced reliance on organic solvents in production, high stability under in vivo conditions, and broad applicability.[3] It consists of structured solid lipid matrix surrounded by lipid and surfactant shells, enabling the encapsulation of drugs within the solid lipid matrix. They are ideal carriers for lipophilic drugs due to their superior physiological stability compared to other lipid-based nano systems.

Additionally, SLNs are made from biodegradable materials and can be produced using a fast, scalable, and efficient manufacturing process.[5]Due to their organized solid lipid core, SLNs often exhibit limited ability to incorporate drugs, which limits their efficiency in drug delivery. Additionally, they may exhibit quick initial delivery and encounter instability factors over time, including crystallization of the lipid matrix and possible drug leakage.[6]

This review focuses on providing an overview of the composition, formulation methods and evaluation strategies of Nanostructured Lipid Carriers (NLCs). It further emphasizes their role as promising nanocarriers for therapeutic delivery, highlighting biomedical applications and recent patent developments.

1.1. NEED AND CHARACTERISTICS OF NANOSTRUCTURED LIPID CARRIERS:

In 1999, a second-generation lipid nanoparticle known as Nanostructured Lipid Carriers (NLCs) was introduced to address the limitations of SLNs. Nanostructured Lipid Carriers (NLCs) preserve the advantages of conventional lipid-based delivery systems but demonstrate improved drug-loading potential and superior stability relative to SLNs.[7] Owing to these favorable attributes, NLCs were first introduced into the cosmetic industry in 2005 and are currently incorporated into a wide range of

commercial formulation. However, despite their high drug encapsulation efficiency and favorable characteristics, their full potential in pharmaceutical drug delivery is yet to be realized.[8]

It is composed of a binary mixture of solid and liquid lipids, with an average particle size ranging from 10 to 500 nm. Typically, the solid and liquid lipids are combined in ratios ranging from 70:30 to as high as 99.9:0.1.[9] It primarily aims to improve the solubility and bioavailability of poorly soluble drugs.[10] This system provides multiple benefits such as compatibility with biological systems, ability to degrade naturally, low risk of immune response, improved drug incorporation, higher stability, sustained release characteristics, and ease of preparation with potential for large-scale production. These benefits make NLCs highly suitable for effective drug delivery applications.[11]

They enable controlled drug release, providing sustained therapeutic effects and reducing side effects by maintaining drug levels within the optimal therapeutic range.[12]The nanostructure of NLCs facilitates effective drug penetration, thereby enhancing drug bioavailability at the target site and leading to improved therapeutic efficacy. Additionally, their flexible composition allows for the incorporation of diverse lipids, surfactants, and active agents, enabling the development of tailored and optimized drug delivery formulations.[13]

NLCs are versatile nanocarriers capable of delivering both hydrophilic and lipophilic drugs. They have gained recognition as promising delivery systems across various routes, including oral, parenteral, ocular, pulmonary, topical, and transdermal administration. More recently, their potential has expanded into areas such as brain targeting, chemotherapy, gene therapy, as well as applications in the food industry, cosmeceuticals, and nutraceuticals.[11]

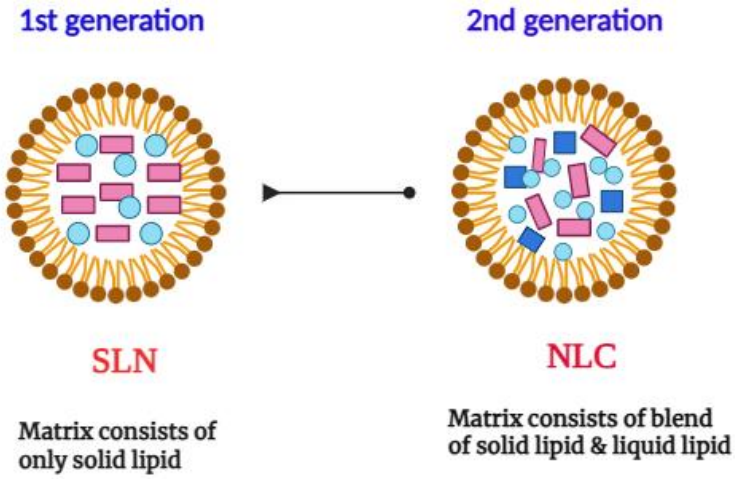

Figure 1: Generation of lipids

1.2. STRUCTURE AND TYPES OF NLCs:

Variations in lipid content and formulation parameters result in changes to the core structure and distribution of solid and liquid lipids. Based on these differences, Müller et al. classified NLCs into three distinct types.

1.2.1. NLC Type I:

It is also known as Imperfect Crystal Model, which features a highly disordered lipid matrix containing numerous voids and spaces that allow the accommodation of drug molecules in amorphous clusters. The incorporation of liquid lipids (oils) into solid lipids generates structural irregularities within the matrix. Due to the variability in fatty acid chain lengths and the presence of mono-, di-, and triacylglycerols, the matrix cannot form a well-ordered crystalline structure. While incorporating spatially different lipids enhances drug-loading capacity, this model typically exhibits lower entrapment efficiency.[14, 15]

1.2.2. NLC Type II:

This system, often referred to as the Multiple Type Model, represents an oil/lipid/water arrangement. Given that hydrophobic drugs typically exhibit greater solubility in liquid lipids compared to solid lipids, this principle facilitated the evolution of Type II NLCs containing a higher proportion of liquid lipids. At lower concentrations, oil droplets are uniformly dispersed within the solid lipid matrix. However, when the amount of liquid lipid exceeds its solubility, phase separation occurs, forming small oil nano-compartments surrounded by the solid lipid matrix. This model offers several advantages, including high drug entrapment efficiency, controlled drug release, and reduced drug leakage.[15, 16]

1.2.3. NLC Type III:

It is also known as Amorphous Type model. This type is formed by incorporating solid lipids that retain the alpha polymorph after solidification and storage, along

with liquid lipids or oils. This combination results in an amorphous core structure. In contrast, solid lipids that transition to the beta polymorph form a crystalline matrix. The amorphous type offers a significant advantage, as it avoids the formation of an ordered crystalline structure, allowing the drug to remain uniformly embedded within the lipid core, thereby minimizing drug expulsion during storage.[17]

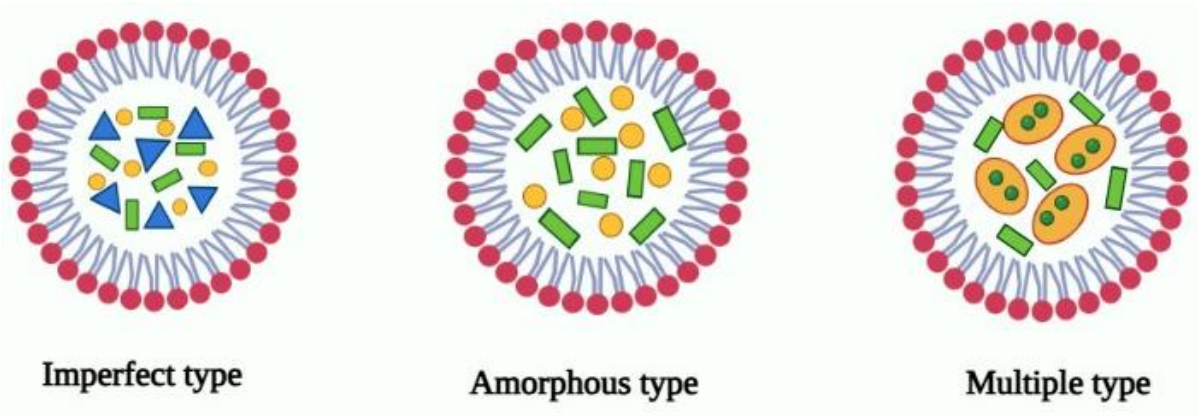

Figure 2: Types of Nanostructured Lipid Carriers

1.3. ADVANTAGES OF NLCs:

- NLCs exhibit excellent biocompatibility and are relatively easier to validate and obtain approval from regulatory agencies.
- NLCs are capable of simultaneously delivering both lipophilic drugs and hydrophilic drugs.
- Compared to other available carriers, NLCs offer superior drug delivery with higher drug-loading capacity.
- The majority of lipids used in NLCs are biodegradable, making them safe and suitable for sustained and controlled drug delivery.
- NLCs offer higher drug loading capacity due to the imperfect lipid matrix structure and enhanced solubility of the drug in the liquid lipid phase.
- NLCs reduce drug expulsion over time by forming an amorphous lipid matrix through the addition of liquid oils, which prevents crystallization during storage.
- They offer greater flexibility in controlling drug release by adjusting the types and quantities of liquid lipids and surfactants used in the formulation.[18-22]

2. ROLE OF EXCIPIENTS IN NLCs:

Lipids serve as the primary component of NLCs, significantly influencing drug loading capacity, formulation stability, and sustained release behavior. Lipid nanoparticle dispersions are typically composed of various lipid materials such as fatty acids, glycerides, and waxes.[23] Most of these lipids, excluding cetyl palmitate, are classified as Generally Recognized as Safe (GRAS) and are physiologically well-tolerated. Therefore, careful selection of suitable lipids is crucial before their use in the formulation of lipid nanoparticle dispersions.[16] Considering the lack of reliable guidelines, empirical values, like the drug's solubility in the lipid, have been suggested to be a significant factor for selecting the right lipid. Lipids with longer fatty acid chains crystallize more slowly compared to those with shorter chains.[16, 24, 25]

2.1. SCREENING OF EXCIPIENTS:

The initial step in developing NLC formulations involves lipid screening, assessing the drug's solubility in various lipids. This is crucial, as the drug's solubility in lipid media directly influences its loading capacity, encapsulation efficiency, and the overall effectiveness of the resulting Nanostructured lipid carriers. [26, 27]

2.2. SOLID LIPID:

Solid lipids are those that remain in a solid state at both room and body temperatures.[28]The solid lipid serves as the core of the lipid nanoparticle, creating a matrix that can encapsulate one or more active ingredients. These lipids are designed to solidify (after processing at temperatures above their melting point) or to precipitate (when formulated using an organic solvent that is later removed). This results in the formation of crystalline platelets or spherical particles with reduced size.[29]

A higher proportion of solid lipid in the formulation supports sustained drug release, especially when the drug is embedded within the particle core. It also helps protect the drug from environmental factors that could cause degradation. Conversely, lipid nanoparticles with reduced crystallinity tend to be more physically stable, maintaining consistent particle size and distribution. More importantly, their limited polymorphic transitions minimize the risk of drug expulsion due to changes in the crystalline structure of the solid lipid.[30]

Table 1: Classification of Solid Lipids with their Composition and Examples[29, 31]

Lipid excipients	Chemical composition	Examples
Waxes	Esters of fatty acids & long-chain alcohols	Carnauba wax, beeswax, cetyl palmitate, paraffin
Vegetable Oils	Triglycerides, free fatty acids, phospholipids	Hydrogenated cottonseed oil, hydrogenated soybean oil
Polyoxylglycerides	Glycerides, fatty acid esters, PEG	Gelucire® 50/02, Gelucire® 50/13
Fatty Acids	Saturated linear carboxylic acids with a chain length of C12 or greater.	Palmitic acid, stearic acid, behenic acid
Triglycerides	Glycerol esters composed of three (monoacid) saturated, straight-chain fatty acids	Glyceryl tripalmitate (Dynasan® 116), glyceryl tristearate (Dynasan® 118)
Partial Glycerides	Mono and diglycerides are glycerol esters containing one or two saturated, straight-chain fatty acids with oneortwo free hydroxyl groups, respectively. They may also include a mixture of mono-, di-, and triglycerides.	Glyceryl distearate (Precirol® ATO 5), glyceryl monostearate, Compritol®
Fatty Alcohols	Saturated linear primary alcohols having a chain length of C12 or longer.	Cetostearyl alcohol, cetyl alcohol

2.2.1. Selection of Solid Lipid:

Solid lipid selection was based on the solubility of the drug, determined by the formation of a visually clear or transparent homogeneous solution without visible drug crystals in the lipid melt. The maximum amount of drug that could be dissolved in 1 g of each solid lipid was evaluated by incrementally adding 1–2 mg of drug to the molten lipid. To simulate the conditions used during lipid nanoparticle formulation, each mixture was thermostatically maintained at 5–10 °C above the lipid's melting point and stirred continuously for 1 hour. Drug solubility was visually assessed by checking for complete dissolution in the melt. The mixtures were then allowed to cool and stored in the dark at room temperature for further analysis. Drug solubility in the lipid is a key factor influencing the encapsulation efficiency of lipid nanoparticles, and higher solubility typically results in greater encapsulation efficiency in the final formulation. [32-35]

2.3. LIQUID LIPID:

Introducing a liquid lipid into the solid framework disrupts the structural order, resulting in lower crystallinity. Additionally, liquid lipids generally offer higher drug solubility than their solid counterparts.[36]Liquid lipids are substances with low melting points that stay in a liquid form at room or surrounding temperatures.[37]

The physical and chemical traits of liquid lipids, such as carbon chain length, thickness (viscosity), greatly affect the features of nanostructured lipid carriers (NLCs). Liquid lipids with extended carbon chains, like glyceryl trioleate, glycerol tricaprylate, and decyl octadec-9-enoate, usually lead to the creation of nanoparticles with smaller sizes compared to lipids with shorter chains.[38]

Table 2: Category of Liquid Lipids based on Origin, Chain Length, and Type

Category	Chain Length	Type	Examples
Natural Oils	Medium (C8–C12)	Triglycerides/Oils	Coconut oil, Palm kernel oil
	Long (C14–C22)	Vegetable oils	Olive oil, Castor oil, Sunflower oil, Soybean oil, Corn oil, Peanut oil, Jojoba oil, Grapeseed oil, Sesame oil
Fatty Acids	Medium (C8–C12)	Saturated	Caprylic acid, Capric acid, Lauric acid
	Long (C14–C22)	Unsaturated/Saturated	Oleic acid, Linoleic acid, Linolenic acid, Stearic acid, Palmitic acid
Semi-Synthetic Lipids	Medium (C8–C12)	MCTs / Esters	Caprylic/Capric triglycerides (Miglyol® 812), Glycerol tricaprylate, Labrafac™ CC, Triacetin
	Long (C14–C22)	Esters	Glyceryl trioleate, Decyloleate, Ethyl oleate, Myritol® 318
Synthetic Lipids	Medium/Long	Esters/PEGylated oils	Isopropyl myristate (IPM), Isopropyl palmitate (IPP), PEG-oleate, Propylene glycol dicaprylate/dicaprate (Labrasol®)
Fatty Alcohols & Esters	Long (C12–C18+)	Fatty alcohols	Cetyl alcohol, Stearyl alcohol, Lauryl alcohol, Myristyl myristate, Oleyl alcohol, Lauryl lactate

2.3.1. Selection of Liquid Lipid:

The liquid lipid in NLC dispersions was selected based on its effectiveness in dissolving the drug. The solubility assessment method followed was similar to those commonly employed in micro-emulsion or self-emulsifying drug delivery systems.[39]

A series of fixed volumes (1 mL) of various liquid lipids were placed separately into screw-capped tubes. An excess amount of drug (up to 2 mg) was added to each tube. The mixtures were shaken for 24 hours at 37°C and 150 rpm using an orbital shaker, water bath shaker, or vortex mixer. After incubation, the samples were centrifuged at 5000 rpm for 30 minutes to separate the undissolved drug. The resulting supernatant was suitably diluted, and drug solubility was analyzed using either HPLC or a UV-Vis spectrophotometer. [33, 40, 41]

2.4. SOLID-LIQUID LIPID COMPATABILITY:

The compatibility and miscibility of solid and liquid lipids were assessed using optical microscopy, macroscopic analysis, and the filter paper test. Solid lipids with high drug affinity were mixed with liquid lipids in a 1:1 ratio, melted, shaken, and allowed to congeal at room temperature. Visual inspection of the congealed lipid mass ensured that no phase separation occurred. For microscopic evaluation, a drop of the molten mixture was placed on a hot microscope slide, covered with a coverslip, and allowed to recrystallize. In the filter paper test, the mixture was cooled without a coverslip; the presence of oil stains indicated poor miscibility, while their absence confirmed good compatibility. These methods ensured the selection of homogeneous lipid combinations suitable for NLC formulation.[41, 42, 43]

2.5. SELECTION OF SOLID–LIQUID LIPID RATIO:

The proportion of solid to liquid lipids was selected according to the melting behaviour of their mixtures. Blends with ratios ranging from 90:10 to 10:90 (solid: liquid) were prepared by co-melting the lipids for one hour, followed by solidification at ambient temperature. The melting points of the resulting mixtures were initially determined using the capillary method. To confirm the optimal composition, Differential Scanning Calorimetry (DSC) was performed. For this analysis, 5 mg samples of both the lipid blends and the pure solid lipid were examined using a DSC6 differential scanning calorimeter (Perkin-Elmer), with a heating rate of 5 °C/min over a temperature range of 30–100 °C. [41, 42]

2.6. SURFACTANT:

Surfactants are essential for stabilizing lipid nanoparticles and play a key role in modulating various characteristics of the colloidal system, such as its viscosity and its effectiveness in dissolving water-insoluble compounds.[44] The HLB value is closely associated with solubility, reflecting the balance between the size and strength of the surfactant's hydrophilic and lipophilic groups.[45] The required HLB (rHLB) of the final dispersion is mainly influenced by the HLB of the lipid and that of the surfactant (including any cosurfactant, if present), and is calculated using the following formula.

$$rHLB = [\%_{Lipid}\, x HLB_{Lipid}] = [\%_{Surfactant} x\, HLB_{Surfactant}] + [\%_{Cosurfactant} x HLB_{Cosurfactant}]$$

Surfactants	Examples
Hydrophilic	Pluronic® F68 (poloxamer 188), Pluronic® F127 (poloxamer 407)polyvinyl alcohol, trehalose, sodium deoxycholate, sodium glycocholate, sodium oleate, Polysorbate (Tween 20, Tween 80), Polyethylene glycol (PEG)
Lipophilic	Span 40 (Sorbitan monopalmitate), Span 60 (Sorbitan monostearate), Span 80 (Sorbitan oleate), Cetyl alcohol, Stearyl alcohol, Isopropyl myristate (IPM), Caprylic/Capric Triglyceride (e.g., Miglyol 812)

2.6.1. Selection of Surfactant:

Surfactants for NLC preparation were chosen based on their ability to emulsify the solid–liquid binary lipid (SLB) mixture. To evaluate this, 100 mg of SLB was dissolved in 3 mL of methylene chloride and added to 10 mL of a 5% surfactant solution under magnetic stirring. The organic solvent was then evaporated at 40°C, and the resulting suspension was diluted tenfold with Milli-Q water. The clarity of the samples was assessed by measuring their percentage transmittance using a UV spectrophotometer.[41, 42]

3. PREPARATION TECHNIQUES AND CATEGORIES OF NLCs:

Several techniques are employed for the production of NLCs, which can be grouped into three categories depending on the amount of energy they require.

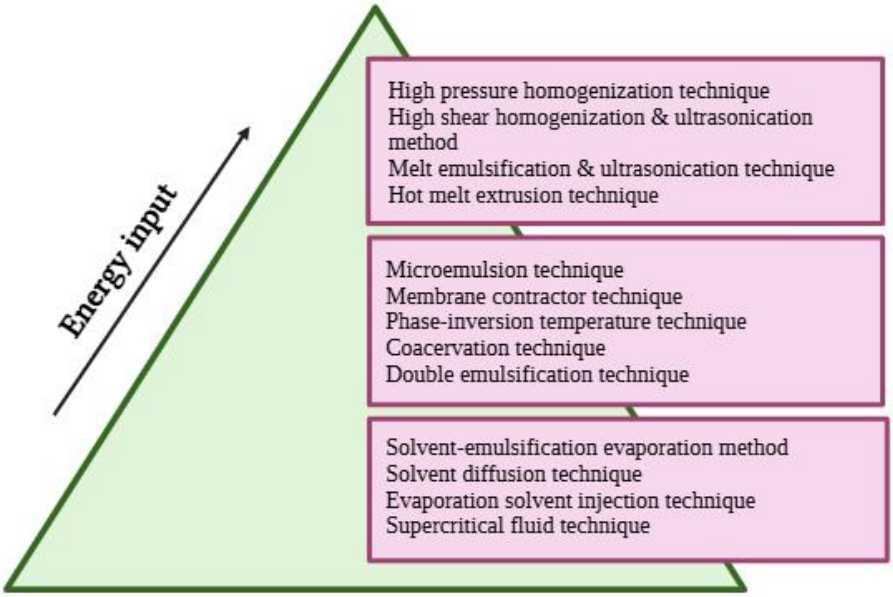

Figure 3: Preparation Techniques of NLCs Based on Energy Input

3.1. ENERGY-INTENSIVE METHODS:

Several techniques are used to produce NLCs, and many of them demand high energy, such as high-pressure homogenization (HPH), high-shear homogenization/sonication, supercritical fluids, and microwave-based methods.

3.1.1. High pressure homogenization technique:

This method is regarded as one of the most preferred techniques since no solvents are required during preparation. It is considered a reliable and efficient approach for large-scale production of NLCs, as it yields highly stable particles without the need for organic solvent addition.[46, 47]

Hot homogenization: In this method, the drug is first incorporated into a molten lipid mixture, which is then dispersed in a heated aqueous surfactant solution using high-speed stirring. The resulting pre-emulsion is subjected to high-pressure homogenization, and upon cooling to room temperature, the Nano emulsion solidifies into NLCs. Despite its effectiveness, this method has certain drawbacks, including possible thermal degradation of heat-sensitive drugs, reduced emulsification efficiency of some surfactants at high temperatures, and relatively low drug encapsulation efficiency. This occurs because, at elevated temperatures, the drug may partition between the lipid and aqueous phases, leading to its leakage into the aqueous medium.[48]

Cold homogenization: It involves solidifying the molten lipid–drug mixture through rapid cooling using liquid nitrogen or dry ice. The solidified mass is then ground into fine particles and dispersed in a chilled aqueous surfactant solution, after which it undergoes high-pressure homogenization. This technique helps to minimize the limitations associated with hot homogenization, such as thermal degradation of drugs and surfactants, while also enabling control over the crystallization process to achieve the desired crystal structure. However, compared to hot homogenization, it often results in larger particle sizes and greater heterogeneity in the final product.[49]

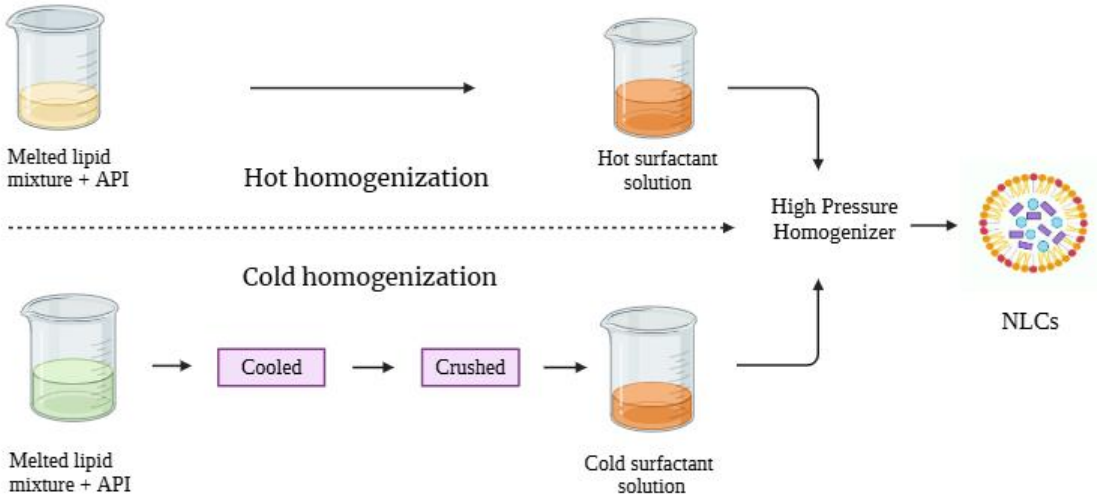

Figure 4: High pressure homogenization technique

3.1.2. High shear homogenization and ultrasonication method:

In this technique, the API is dissolved in the melted oil phase and processed using high-speed homogenization to produce a nano-dispersion. A surfactant solution (such as pluronics, soy lecithins, and tween, span, or polyethoxylated monoglycerides) is preheated to the same temperature as the lipid and then added gradually to ensure uniform mixing. Higher stirring speeds typically yield smaller particle sizes. To further reduce droplet size and avoid aggregation, probe sonication is commonly applied, where ultrasonic cavitation enhances homogenization, dispersion, and emulsification. Key parameters such as lipid–surfactant ratio, stirring speed, and sonication time must be optimized for reproducible, nanosized carriers. However, limitations include poor dispersion due to microparticles causing storage instability and the possibility of metal contamination from equipment.[50-52]

3.1.3. Melt emulsification homogenization technique:

In the melt emulsification method, the process closely resembles high-shear homogenization. Here, the solid and liquid lipids along with the API are homogeneously blended and introduced into the surfactant solution using sonication. Subsequent cooling of the dispersion to a reduced temperature results in the formation of solidified NLCs. The primary benefit of this approach lies in its ability to avoid heat exposure. This procedure is acknowledged as a straightforward approach to NLC formation.[53, 54]

3.1.4. Hot melt extrusion technique:

In the hot melt extrusion technique, the drug and solid lipid mixture is fed into an extruder barrel using a volumetric feeder, while liquid lipid and aqueous solutions are simultaneously added via a peristaltic pump at the extrusion temperature. The blend is extruded at the melting point to form a pre-emulsion, which is then sonicated to reduce the particle size and produce nanostructured lipid carriers (NLCs).[55]

3.2. LOW ENERGY METHODS:

3.2.1. Micro emulsion technique:

In this method, the lipid carrier is heated just above its melting point, followed by the addition of drug, auxiliary emulsifier, and preheated deionized water to form a clear, thermodynamically stable micro emulsion. The hot micro emulsion is then quickly dispersed into ice-cold water (0–4 °C) under gentle stirring, producing NLC dispersion. Dilution breaks the micro emulsion into a Nano emulsion of ultrafine particles, and the internal lipid droplets recrystallize to generate nanosized carriers. The typical ratio of hot micro emulsion to cold water ranges from 1:10 to 1:50. This technique is advantageous due to its simplicity, but requires large amounts of emulsifiers and co-emulsifiers, which is a major limitation.[54, 56]

3.2.2. Membrane contractor technique:

In this technique, lipids are forced through membrane pores under pressure, maintaining temperatures above their melting point to generate fine droplets. Simultaneously, the aqueous phase circulates within the membrane, carrying the droplets formed at the pores. Upon cooling to room temperature, these droplets solidify into lipid nanoparticles (LNPs). The characteristics of the LNPs, including size and lipid incorporation, are determined by several factors: flow velocity of the aqueous phase, temperatures of both lipid and aqueous phases, pore size of the membrane, and applied lipid phase pressure.[57]

3.2.3. Phase-inversion temperature technique:

This technique is a novel, cost-effective, and solvent-free approach for preparing nanostructured lipid carriers (NLCs).It is based on the principle of phase inversion, which depends on the temperature-sensitive hydrophilic–lipophilic balance (HLB) of surfactants. At elevated temperatures, surfactants exhibit lower HLB values, favoring changes in the emulsion type.[58]By applying controlled heating–cooling cycles (85°C–60°C repeated thrice), the system passes through the phase inversion zone. During this stage, the emulsion alternates between oil-in-water (o/w) and water-in-oil (w/o) states. The process begins with mixing lipid, surfactant, and water in optimized ratios. The mixture is then gradually heated at 4°C per minute until it reaches 85°C.After completing three thermal cycles, the system is subjected to rapid cooling. This is achieved by diluting it with ice-cold water (0°C), introducing an irreversible shock. The sudden phase inversion drives the formation of nanocapsules. Gentle magnetic stirring for a few minutes prevents particle aggregation. The outcome is a stable, transparent dispersion (<25 nm) ideal for encapsulating thermo labile bioactive compounds without the use of solvents.[59]

3.2.4. Coacervation technique:

The coacervation technique is a novel, solvent-free method that allows the encapsulation of even thermosensitive drugs without requiring costly equipment or harmful solvents. It involves the slow interaction of a micellar solution of fatty acid sodium salt with an acid solution, in the presence of a suitable amphiphilic polymer stabilizer.

3.2.5. Double emulsification technique:

The double emulsification method, adapted from solvent emulsification–evaporation, is particularly suitable for formulating lipid nanoparticles encapsulating hydrophilic drugs. In this approach, the stabilizer and drug are incorporated into the inner aqueous compartment of a water-in-oil-in-water (W/O/W) emulsion. Because these systems generally exhibit a larger particle size than solid lipid nanoparticles (SLNs), they are commonly referred to as lipospheres.[60]

3.3. VERY LOW ENERGY OR ORGANIC SOLVENT DEPENDENT FABRICATION METHODS:

3.3.1. Solvent-emulsification evaporation method:

The drug and a blend of solid and liquid lipids are dissolved in a water-immiscible organic solvent before being emulsified into an aqueous solution containing emulsifiers, creating an oil-in-water emulsion. The organic solvent is then evaporated under reduced pressure, resulting in lipid precipitation and nanoparticle formation in the aqueous phase. This approach prevents thermal damage but is limited by the use of organic solvents. The particle size typically ranges between 30 and 100 nm, depending on the choice of lipids and surfactants.[61]

3.3.2. Solvent diffusion technique:

This method, a variation of solvent evaporation, employs a water-miscible organic solvent to dissolve the lipid and active compound, forms an oil-in-water emulsion with a surfactant solution, and achieves solvent removal through aqueous dilution (1:10), resulting in Nano precipitation, with the solid phase finally recovered by ultrafiltration or lyophilization.[62, 63]

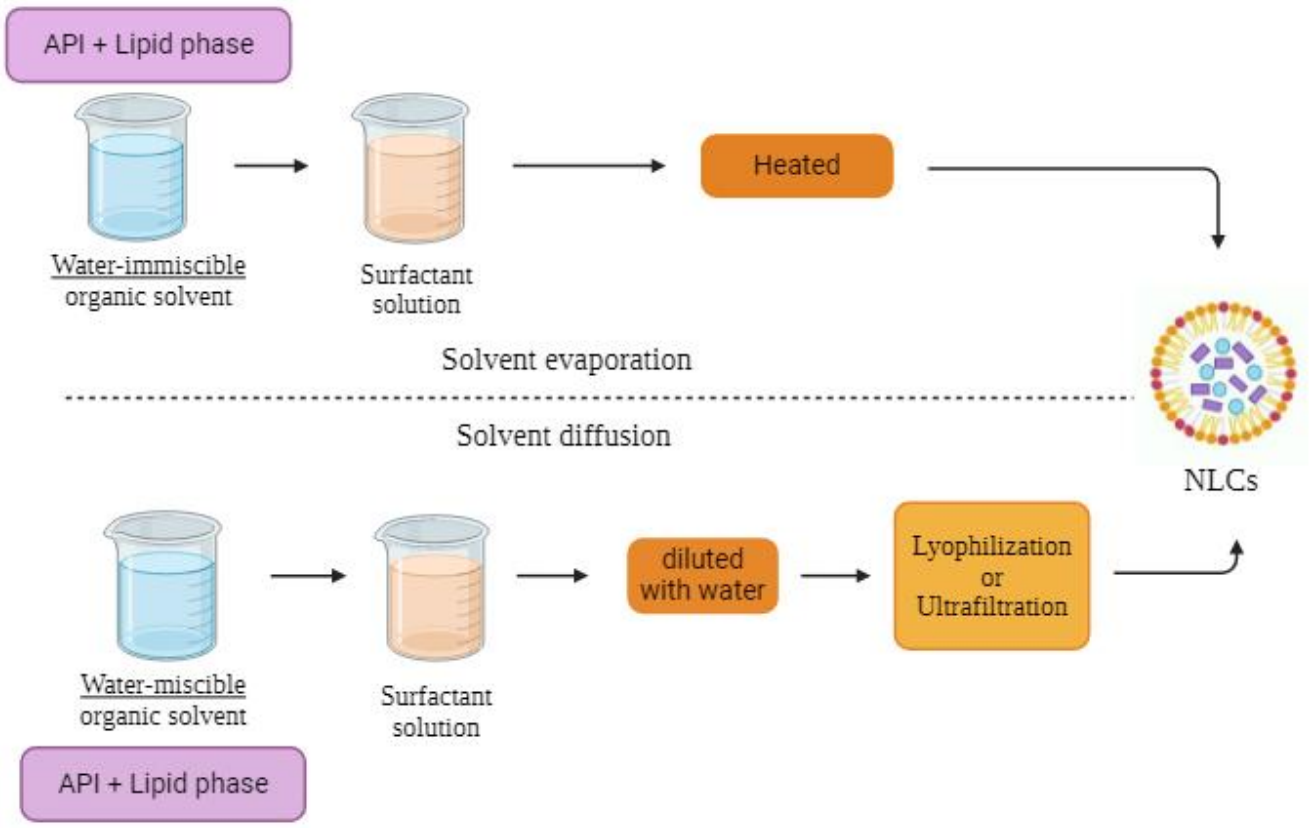

Figure 5: Comparative Assessment of Solvent Evaporation and Diffusion Techniques

3.3.3. Evaporation solvent injection technique:

In this approach, lipids are dissolved in a water-compatible organic solvent and then quickly introduced into an aqueous surfactant solution under continuous stirring. The rapid diffusion of solvent into the aqueous medium causes lipid precipitation, leading to the formation of nanostructured lipid carriers. Particle size is influenced by both solvent transfer rate and stabilizer concentration. The resulting dispersion is filtered to remove unincorporated lipid, offering a straightforward, efficient, and equipment-free method that utilizes pharmaceutically acceptable solvents.[64, 65]

3.3.4. Supercritical fluid technique:

This method involves dissolving the lipid and drug in an organic solvent, such as chloroform, with a suitable surfactant to form a homogeneous organic phase. This phase is dispersed into an aqueous solution, which may include a co-surfactant, and subjected to high-pressure homogenization to create a stable oil-in-water emulsion. The emulsion is continuously fed at a constant rate into an extraction column, where a supercritical fluid is simultaneously introduced counter currently under controlled temperature and pressure. This continuous solvent extraction process effectively removes the organic solvent, yielding well-formed lipid nanoparticle dispersions.[60, 63]

3.4. LYOPHILIZATION OF NLCs:

The free-drying (lyophilization) approach has been used to stabilize the NLCs. Extending the product's storage life and protecting it from both chemical and physical deterioration are two goals of lyophilization.

Consequently, it is simple to produce a solid-state material using the method of lyophilization, and it would easily re-disperse when needed. The sublimation

concept, often known as the dehydration process, is the foundation of lyophilization in general. It states that water moves directly from a solid state (ice) to a gaseous form without first being liquid.[66]

Cryoprotectants or lyoprotectants are stabilizing agents used in the lyophilization process which protect the formulation during freeze-drying (cryoprotectant) from the pressures of drying and freezing (lyoprotectant). Cryoprotectants, such as mannitol, trehalose, fructose, sorbitol, lactose, glucose, sucrose, and aerosil, are included in 5–15% w/w concentration that protect the product from the high stress produced during the lyophilization process.[67]

Freeze drying is a reliable method as it preserves the molecular integrity of the product. Cryoprotectants vitrify at a specific glass transition temperature (Tg), immobilizing nanoparticles within a glassy matrix to prevent aggregation and protect against ice crystal damage. Besides enhancing the long-term stability of nanostructured lipid carriers (NLCs) during storage, cryoprotectants also act as bulking agents and help maintain the formulation's tonicity, especially when the concentration is low.[68]

During storage, NLCs may aggregate or degrade, making stability crucial. Cryoprotectants like mannitol and trehalose are commonly used during lyophilization to prevent aggregation and preserve physical properties. For example, mannitol improved the stability of Tilmicosin NLCs, while trehalose proved most effective in stabilizing lopinavir NLCs by minimizing aggregation and offering higher glass transition temperature and reduced chemical interactions, enhancing nanoparticle stability during freeze drying.[69]

3.5. CHARACTERIZATION OF NLCs:

3.5.1. Particle Size, Polydispersity Index (PDI), and Zeta-Potential:

Particle size is crucial for NLC bioavailability, permeation, and cellular uptake, typically ranging from 50 to 500 nm. Dynamic light scattering (DLS) measures the hydrodynamic diameter (Z-average), based on Brownian motion-induced light intensity fluctuations.

The polydispersity index (PDI), ranging from 0 (monodisperse) to 1 (heterogeneous), assesses size uniformity, with values below 0.3 indicating a homogeneous dispersion, ideal for consistent drug release.[70] Zeta potential, calculated from electrophoretic mobility using the Helmholtz-Smoluchowski equation, reflects surface charge and colloidal stability. Values near or below -30 mV indicate sufficient electrostatic repulsion to prevent aggregation. Dilution with deionized water before measurement reduces multiple scattering effects.[71]

Particle size (50–500 nm) critically influences the bioavailability, permeation, and uptake of NLCs. It is usually measured by dynamic light scattering (DLS) to determine the hydrodynamic diameter. Size is governed by lipid composition, surfactant levels, and processing variables such as homogenization and sonication. Incorporation of liquid lipids reduces size compared to SLNs, while drug loading may enlarge particles due to increased viscosity. Particles below 200 nm are optimal as they improve absorption, stability, and dissolution of poorly soluble drugs.[70, 72]

3.5.2. Properties of Morphology:

Drug release kinetics and interactions with biological membranes are influenced by surface shape. After dilution, drying, and gold/palladium coating, spherical particles with smooth surfaces are visible by scanning electron microscopy (SEM), which visualizes the shape and topography of nanoparticles. This validates the integrity of the nanostructured core and verifies the lack of aggregation. Additionally, its homogeneous dispersion precludes sensory change in applications such as food fortification.[73]

3.5.3. Encapsulation efficiency (EE) and drug loading (DL):

These are critical parameters for evaluating nanostructured lipid carriers (NLCs). EE reflects the proportion of drug successfully incorporated into nanoparticles, whereas DL indicates the amount of drug relative to the total weight of lipids and entrapped drug. High EE ensures minimal drug wastage, while higher DL contributes to efficient carrier design and therapeutic effectiveness.[74]

The parameters are calculated using the following equations:

$$\%EE = \frac{\text{Total amount of drug added} - \text{Amount of drug in supernatant}}{\text{Total amtount of drug added}} \times 100$$

$$\text{Drug content} = \frac{\text{Amount of drug obtained}}{\text{Total amount of drug added}} \times 100$$

Experimentally, EE and DL are determined by separating free drug from nanoparticles using centrifugation or ultrafiltration, followed by quantification through (HPLC). Formulation variables, such as lipid composition, drug-to-lipid ratio, and surfactant concentration, significantly influence EE and DL, which are crucial for designing efficient NLC-based drug delivery systems.[75]

3.5.4. FTIR Characterization of NLCs - Procedure:

Sample preparation. Disperse the NLC samples and relevant controls (blank solid–lipid nanoparticles, NLC with liquid lipid only, drug-loaded NLC, and the physical components such as the pure drug/essential oil) and convert them to dry powders prior to FTIR. In the referenced workflow, dispersions were snap frozen, stored at -80 °C, and lyophilized without cryoprotectant (48 h; chamber pressure ~3.0 mbar; shelf ~-18 °C) to obtain free flowing solids suitable for pellet preparation.

Pellet formation: For transmission measurements, intimately mix the dried sample with spectroscopic-grade KBr and compress the blend into transparent pellets using a hydraulic press.[76]

FTIR analysis was conducted to evaluate potential drug–excipient interactions. Samples were prepared using the KBr disc method, followed by placement in the FTIR

instrument's sample holder. Spectra were recorded over a wavelength range of 4000 to 400 cm^{-1}.[77]

3.5.5. Differential Scanning Calorimetry (DSC):

It is used to assess the thermal behavior and crystallinity of nanostructured lipid carriers (NLCs). About 2–3 mg of the sample is sealed in a hermetic aluminum pan and heated from 20–100 °C at 5 °C/min using a DSC instrument (e.g., TA Q20), with an empty pan as reference. Each formulation undergoes three thermal cycles for reproducibility. Thermograms provide data on onset temperature, peak melting point, and enthalpy changes, indicating lipid crystallinity. A shift in peak temperature or reduced enthalpy suggests decreased crystallinity due to liquid lipid incorporation, aiding in evaluating structural stability and encapsulation efficiency.[78]

3.5.6. *In vitro* Drug Release of NLCs:

The *in vitro* release of drugs from nanostructured lipid carriers (NLCs) is generally investigated using a dialysis bag diffusion technique. In this method, a fixed volume of NLC dispersion containing an accurately measured amount of drug is placed in a pre-soaked dialysis membrane (molecular weight cut-off 12–14 kDa). The sealed bag is immersed in a release medium, typically phosphate buffer saline (PBS, pH 7.4) or simulated physiological fluids, maintained at 37 ± 0.5 °C under constant stirring to ensure sink conditions. At predetermined intervals, aliquots are withdrawn from the receptor compartment and replaced with fresh medium to maintain volume consistency. The collected samples are filtered and analyzed spectrophotometrically or by HPLC to quantify the released drug.

This procedure allows the assessment of release kinetics and mechanisms, often fitted to mathematical models such as zero-order, first-order, Higuchi, or Korsmeyer–Peppas equations to elucidate the release behavior. The dialysis method provides a simple yet effective approach to mimic drug diffusion across biological membranes, although alternative systems like Franz diffusion cells or USP dissolution apparatus may also be employed depending on formulation characteristics.[79]

3.5.7. Stability Studies:

Stability assessments monitor changes in particle size, PDI, and zeta-potential over time (e.g., 30 days at 6°C and 25°C). NLCs with glycerol distearate cores exhibited superior resistance to phase separation compared to monostearate variants, underscoring the role of lipid composition in preventing aggregation or crystallization. This parameter is vital for shelf-life prediction and real-world applicability in diverse storage conditions.[70]

In brain tumor targeting, NLCs demonstrate enhanced stability and biocompatibility, attributed to their solid matrix at ambient temperatures, which minimizes toxicity and supports sustained release.[62] Across routes like oral, nasal, and ocular, characterization emphasizes biocompatibility and scalability, with NLCs outperforming SLNs in drug retention due to their amorphous or multiple-type structures.[80]

3.6. APPLICATIONS OF NLCs:

3.6.1. Enhancement of bioavailability of lipophilic drugs:

Nanostructured lipid carriers (NLCs) are advanced delivery systems designed to enhance the bioavailability of poorly water-soluble, lipophilic drugs. By combining solid and liquid lipids, NLCs create a less ordered matrix that improves drug loading and stability over solid lipid nanoparticles (SLNs). Their small size (<100 nm) increases surface area, aiding drug solubilization, membrane interaction, and absorption, ultimately enhancing systemic circulation.[81]

NLCs provide controlled, sustained drug release, helping maintain therapeutic levels while minimizing toxicity. Studies with hydrophobic anticancer drugs have shown improved plasma concentrations and reduced side effects. Surface functionalization with targeting ligands or biocompatible polymers enhances site-specific delivery, making NLCs a flexible and effective strategy for overcoming biopharmaceutical challenges, especially in cancer treatment and other targeted therapies.[82]

3.6.2. Oral Administration of NLCs:

Nanostructured lipid carriers (NLCs) offer an effective approach for oral delivery of poorly soluble drugs by improving solubility, absorption, and resistance to gastrointestinal degradation. Their solid–liquid lipid matrix enhances drug loading, stability, and provides controlled release, while surface modifications such as PEGylation or thiolation promote mucus penetration and intestinal uptake. Studies show PEGylated NLCs of trimethoprim/sulfamethoxazole improved permeability and reduced systemic toxicity, NAC-PEG modified curcumin NLCs achieved a marked rise in bioavailability, and tacrolimus NLCs enhanced solubility, lymphatic transport, and systemic exposure. Collectively, these findings demonstrate the versatility of NLCs in boosting therapeutic efficacy and safety across antibiotics, nutraceuticals, and immunosuppressants.[83-85]

3.6.3. Parenteral Delivery Strategies with NLCs:

Nanostructured lipid carriers (NLCs) offer significant advantages for parenteral delivery by combining solid and liquid lipids to enhance drug encapsulation, stability, and release over traditional solid lipid systems. They have been applied to a broad spectrum of agents, including anticancer drugs like paclitaxel for tumor-targeted therapy, amphotericin B with reduced toxicity, diagnostic imaging compounds, antiarthritics, cardiovascular drugs, and even nucleic acids for gene delivery. Surface engineering, particularly PEGylation, minimizes opsonization and prolongs circulation time, while recent advances highlight their role in delivering both synthetic drugs and biologics such as mRNA vaccines. Overall, NLCs enable controlled release, improved bioavailability, and enhanced therapeutic performance in intravenous administration.[86, 87]

3.6.4. Transdermal Drug Delivery Strategies:

Nanostructured lipid carriers (NLCs) are emerging as effective vehicles for topical drug delivery, offering enhanced skin absorption, improved drug protection, and controlled release with reduced irritation for various skin conditions. Allopurinol-loaded NLCs (193 nm, 52% encapsulation) have shown sustained release properties, minimal toxicity to HaCaT cells at concentrations below 10 µg/mL, and superior wound healing in Wistar rats by targeting xanthine oxidase, leading to decreased uric acid and reactive oxygen species production results that surpass conventional treatments and yield no erythema.[88]

For treating hyperpigmentation, N-acetyl glucosamine (NAGA) loaded into NLCs greatly increased retention in the skin and reduced melanin production, performing better than hydroquinone creams, which are known to cause irritation.[89] Tretinoin-NLCs designed with stearic and oleic acids offered sustained release, week-long stability, and absence of skin irritation in preclinical models, demonstrating higher drug loading and bioavailability compared to standard topical gels used for acne and aging.[90]

3.6.5. Cosmetic applications:

In skincare, nanostructured lipid carriers (NLCs) improve the penetration of active compounds like vitamins, antioxidants, and retinoids through the stratum corneum, ensuring better absorption with minimal irritation. Their occlusive action reduces water loss, enhances hydration, and promotes collagen synthesis, supporting anti-aging benefits. By boosting UV protection and enabling controlled, prolonged release, NLCs also enhance sunscreen efficacy. These versatile features make them valuable in creams, serums, and masks, advancing the field of personalized cosmeceuticals.[36, 91-93]

3.6.6. Nose-to-Brain Targeting Using NLCs:

Nanostructured lipid carriers (NLCs) enable efficient nose-to-brain drug delivery by bypassing the blood–brain barrier through olfactory and trigeminal pathways, thereby improving bioavailability while reducing systemic side effects. For instance, atomoxetine-loaded NLC in situ gels showed sustained release (~93% over 12 h), high nasal permeation, and 51.91% brain-targeting efficiency in rats, enhancing dementia therapy outcomes. Similarly, NLC-based hydrogels for Alzheimer's disease protect lipophilic drugs from rapid nasal clearance, allowing direct CNS delivery and mitigating oxidative stress and neuroinflammation. With sizes of 100–200 nm and adaptable surface properties, NLCs maximize brain drug uptake, positioning them as a promising approach for neurodegenerative disease management. [94-96]

4. PATENT STATUS OF NLCs:

S.N.	TITLE	PATENT NUMBER
1	Solid compositions including stabilized lipid nanoparticles and methods of making microneedles comprising same	US2025099371A1
2	Preparation method of cannabidiol Nano lipid carrier with transdermal absorption function	CN119523902A
3	Nanostructure lipid carrier containing hydroxyl resveratrol	CN119499141A
4	High-solubility nanostructure lipid carrier as well as preparation and application thereof	CN119279197A
5	Flurala nanostructure lipid carrier and preparation method thereof	CN119112798A
6	Levamisole nanostructure lipid carrier gel for treating allergic rhinitis	CN119015212A
7	Green synthesis of silver nanoparticles encapsulated in a nanostructured lipid carrier	US12133863B1
8	Nano-structure lipid carrier wrapping hyaluronic acid as well as preparation method and application of nanostructure lipid carrier	CN118873423A
9	Preparation method of diacylglycerol nanostructure lipid carrier loaded with fat-soluble nutrients	CN118592608A
10	Aaloperine nanostructure lipid carrier as well as preparation method and application thereof	CN118370724A
11	Nanostructured lipid system containing besifloxacin, pharmaceutical composition and uses	WO2024098127A1
12	Nanostructure lipid carrier and application thereof	CN117883295A
13	N-[3-(4-fluorophenyl)-isoxazole-5-yl]-methyl rupestonic acid amide nanostructure lipid carrier as well as preparation method and application thereof	CN117815227A
14	Nanoparticles with antibodies for ocular treatment	WO2024160819A1

15	Chitosan interface modified ellagic acid nanostructure lipid carrier and preparation method thereof	CN117398294A
16	Intranasal administration of thermostable RNA vaccines	WO2023228116A1
17	Ketoconazole nanostructure lipid carrier gel and preparation method thereof	CN117122561A
18	Preparation method and application of diglyceride nanostructure lipid carrier hydrogel	CN116725918A
19	Targeted multifunctional nanostructured lipid carriers	US2024156742A1
20	Nanoparticulate Monobenzone for treating melanoma	US2024408214A1

5. CONCLUSION:

Nanostructured lipid carriers (NLCs) are advanced lipid-based nanocarriers that combine solid and liquid lipids to improve drug loading, stability, and controlled release. They are biocompatible, biodegradable, non-toxic, and can encapsulate both hydrophilic and lipophilic drugs for delivery via oral, dermal, ocular, pulmonary, and brain-targeted routes. Their versatility enables surface modifications for site-specific targeting in cancer, infections, neurodegenerative, and genetic diseases. NLCs also enhance skin hydration, wound healing, and act as effective carriers in cosmetics. They can be produced on a large scale using FDA-approved excipients and adaptable methods like high-pressure homogenization. Moreover, NLCs can serve as diagnostic tools in imaging, in addition to therapeutic applications. Despite numerous advantages, clinical use is slowed by toxicity concerns, formulation challenges, and limited human studies. Continued research in multifunctional and safer NLC designs may accelerate their translation into medical and commercial applications.

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