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Nanostructured lipid carriers as a drug delivery system: A comprehensive review with therapeutic applications

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Abstract

Recent advances in nanotechnology have enabled significant developments in health through innovative drug delivery systems. Nanostructured lipid carriers (NLCs) have emerged as a key technology in this field, offering enhanced drug stability, improved loading capacity, and reduced drug leakage compared to traditional solid lipid nanoparticles (SLNs). NLCs, such as ARM-NLC and PIO-loaded NLCs are specifically designed to optimize drug delivery and efficacy. Unlike other nanocarriers, NLCs provide controlled release and targeted delivery, making them highly effective for treating a range of diseases. Their applications include the treatment of skin cancer, Parkinson’s disease, Alzheimer's disease, and breast cancer. The use of surface-engineered nanolayer coatings in NLCs has demonstrated significant improvements in targeting and delivering medications and bioactive substances to infection sites. Both in vitro and in vivo studies have shown promising results regarding the safety and efficacy of these NLC-based drug delivery systems.

Key words: Nanostructured lipid carriers, Skin cancer, Parkinson’s disease, Alzheimer's disease

Introduction

Nanotechnology is used in many fields, including environmental science, medicine, cosmetics, and nutraceutical research [1]. Nanotechnology has become a powerful tool in recent years for tackling the limitations of traditional drug delivery methods [2]. Nanocarriers are colloidal systems with an average diameter of less than 1 micron [3]. Since they have special qualities, such as a high surface-to-volume ratio and nanoscale size, nanoparticles can be employed for medicinal purposes [4]. Their decreased size compared to biological macromolecular medicines or standard chemotherapeutic agents allows them to be coupled with several support components and pharmaceutically active chemicals [5]. These components enable stimulus-based activation, imaging, targeting, and degradation resistance. However, the body processes nanoparticles differently than it does conventional medications [6]. Nanoparticles have distinct biodistribution profiles and hydrodynamic characteristics. It is noteworthy that interactions occurring at the nanobiological level have the potential to be used for better drug delivery [7]. The encapsulating moieties of nanocarriers can be altered to improve their pharmacokinetic and biodistribution characteristics, decrease toxicity, regulate release, improve solubility and stability, and deliver their payload to targeted sites [8]. The physiochemical characteristics of nanocarriers, such as their surface, composition, and shape, can be altered to improve their activities with fewer side effects. Nanostructured lipid carriers (NLCs) present promising advancements in drug delivery systems, yet they face several challenges that hinder their clinical application. These challenges include formulation complexities, stability issues, and biological barriers [9].

Polymeric, lipidic, inorganic nanoparticles, liposomes, nanotubes, nanocomplexes, niosomes, and several other forms are examples of nanocarriers (figure 1) [10]. Nanocarriers' surface characteristics have a major impact on their bioavailability, stability, cellular absorption, and biodistribution [11]. The surface charge expressed by the zeta potential influences the aggregation tendencies of the nanocarrier units, suggests potential electrostatic interactions between them, and helps in the selection of suitable coating materials [12]. There are several biological aspects that are influenced by the shape and aggregation behavior of nanocarriers, such as their half-life, targeting effectiveness, and toxicity [13]. Numerous non-spherical shapes, such as cubes, cones, hemispheres, cylinders, and other complex shapes, have a significant impact on those biological functions [14].

Triglycerides, partial glycerides, fatty acids, and waxes are the constituents of lipid nanoparticles, which are combined with various surfactant combinations [15]. Lipid nanoparticles exhibit effective and targeted drug delivery since their particle size is typically less than 1 μm [16]. Polymer nanoparticles, made of biodegradable and biocompatible polymers, are used in the synthesis of nanosized carriers [17]. Due to their capacity to carry large amounts of pharmaceuticals and to release drugs slowly while preventing their deterioration, their biodegradable nature has drawn much attention as potentially appropriate systems for drug administration [18]. Drug adsorption efficiency and surface quality are enhanced by the introduction of polymer nanoparticles [19].

Polymeric micelles are self-assembling block copolymer carriers made up of a core-shell structure. The essential micelle concentration of polymeric micelles, as well as their size and form, may be controlled by the structural and physical properties of copolymers [20].

The inorganic nanocarriers are gold nanoparticles, carbon nanotubes, quantum dots, mesoporous silicon, and magnetic nanocarriers. Inorganic nanocarriers are used for novel purposes such as cell labeling, imaging, biosensing, targeting, and diagnosis [21].

Lipid based drug delivery system

They are composed of lipids that are both biodegradable and biocompatible and offer pharmaceutical protection, controlled release, and targeted distribution [22]. The ability of these drug delivery systems to incorporate a wide range of therapeutic substances, including growth factors, gene therapy, and cytokines is greater than conventional methods [23].

A variety of drugs, including new chemical entities, proteins and peptides, nucleic acids, and delivery to particular cell locations, can be administered using lipid-based drug delivery systems [24]. Lipid-based drug delivery systems are classified as vesicular systems and lipid nanoparticles [25]. Vesicular drug delivery systems are highly organized assemblies made up of one or more concentric bilayers that arise when amphiphilic building blocks self-assemble in the presence of water [26]. Lipid vesicles have a range of diameters between 40 and 800 nm, which enable them to stick to the lipid matrix of the corneous layer and enhance the number of drug molecules that reach the deeper layers of the skin. Vesicles with a size of ≤70 nm have demonstrated the highest possible delivery of substances, The study highlights that sonication

yields the highest loading efficiency but reduces particle yield, while electroporation produces more loaded particles at lower efficiency [25,26]. The lipid vesicle wall is lipophilic in nature, so it can act as an organic phase for drugs that are poorly soluble in water, and they have better penetration-enhancing qualities. Furthermore, vesicular lipid systems act as a local depot system and do not release quickly [27].

Since 1950, liposomes have been extensively studied as drug vesicular carriers to improve the delivery of drugs to the target areas [28]. The liposome, which has lipid bilayers that resemble a cell's plasma membrane, is a perfect and safe drug delivery vehicle. They have hydrophilic (represented by diamonds in figure 1) and hydrophobic areas (represented by circles in figure 1) that can hold a range of therapeutic substances [29].

Niosomes, also known as non-ionic surfactant vesicles, are tiny lamellar vesicles that are created when cholesterol is combined with nonionic surfactants and then hydrated in aqueous solutions [26]. Niosomes were developed as an alternative to liposomes in order to get over issues with stability, sterilization, and large-scale liposome manufacture [30]. Like liposomes, niosomes have the ability to encapsulate hydrophilic and hydrophobic therapeutics in their respective hydrophilic and bilayer compartments [31]. Additionally, they could enhance medication targeting, improve drug absorption and bioavailability, and improve the pharmacokinetics and biodistribution of therapeutics [32]. Since liposomes and niosomes are not suitable for transdermal drug delivery due to their poor skin permeability and propensity to aggregate and fuse in skin tissues, Gregor Cevc developed a new class of carriers called transfersomes in 1991 [26]. Transfersomes are elastic vesicles with an edge activator and a bilayer serving as their backbone [33]. Transfersome’s superior deformability is attributed to the ideal ratio of phospholipids to edge activators [34]. The edge activator, which increases the vesicles' flexibility and deforming ability while weakening their lipoidal bilayer, is primarily responsible for their elasticity [35].

Ethosomes are suggested as an alternative to traditional liposomes to improve the transdermal permeability of integrated drugs [36]. 20–50% ethanol is mixed with the bilayer (aqueous and lipid) that makes up the structural framework of ethosomes to give them their flexible nature [37]. The changes in temperature of the lipids in the stratum corneum are lowered when ethanol engages with the lipid molecules in the polar head group region [38]. These enhance mobility

and decrease lipid multilayer density, which leads to the drug's delivery into the skin's deep layers. Additionally, ethanol gives vesicles elasticity and softness, which allows for better permeation into the epidermal layer [39].

The utilization of biocompatible and biodegradable lipids has resulted in a significant increase in interest in lipid-based nanocarriers during the past 20 years. Lipid nanoparticles can overcome the drawbacks of polymeric nanoparticles, like cytotoxicity and a lack of appropriate bulk production [40].

The spherical solid lipid nanoparticles (SLNs) have a nanoscale size range of 50–1000 nm [41]. SLNs were developed to provide advantages for biocompatibility, long-term stability, and prevention of medication degradation [42]. SLNs exhibit stable behavior because of the decreased interfacial tension that the emulsifiers (represented by circles in figure 1) provide between the hydrophobic lipidic medium and the aqueous environment [43]. The components of solid lipid nanoparticles (SLNs) range from 0.1% (w/w) to 30% (w/w) of solid lipids or a combination of solid lipids distributed in an aqueous medium [44]. Although a mixture of solid lipids and liquid lipids is used in the ratio of 73:30 up to a ratio of 99.9:0.1 to generate nanostructured lipid carriers, [45]. Both liquid and solid lipids are used in the formation of the NLCs, resulting in unique nanostructures with enhanced stability, drug loading, and release of drug profile modification capabilities [46]. NLCs can protect substances that are vulnerable to light, oxidation, or hydrolysis [44]. Moreover, the NLCs' distinct lipid composition and smaller particle size enable a close association with the stratum corneum, improving drug flow through the skin and increasing drug penetration [47].

Lipid nanoparticles have the potential to significantly enhance a drug's solubility, bioavailability, pharmacokinetic characteristics, intestinal absorption, skin penetrability, and ocular residence duration. This may help the medication cross physiological barriers and lessen negative side effects [48].

Inorganic nanocarrier

Inorganic nanocarriers include gold nanoparticles, magnetic nanocarriers, carbon nanotubes, quantum dots, and mesoporous silica [49]. Inorganic material-prepared nanoparticles are commonly favored because of their malleability, large surface area, crystal structure, ease of

chemical modification, and high-density surface ligand binding [50]. The size, shape, and elemental content of inorganic nanoparticles can be modified to satisfy the needs of therapeutic loading capacity, biocompatibility, extended circulation time, and cellular al., absorption [51]. Inorganic nanocarriers that act as the systems' skeletons have the ability to load and release medications, maintain an intact blood circulation framework, and have good pharmacological and biocompatibility characteristics [50].

Gold nanoparticles have distinctive physicochemical and optical features that make them useful for image-based diagnosis and therapeutic delivery [52]. Gold nanoparticles (NPs) can be readily altered by different functional groups to target ligands and PEG-containing linkers for combining drugs or nucleic acids for delivery to distinctive cells [53]. The capacity of AuNPs to interact with light through SPR has drawn a lot of attention [54]. In cancer therapy, gold has been extensively utilized as a nanomaterial for therapeutic purposes. It is utilized in the biomedical industry for very sensitive biomolecular screening, photothermal therapy-assisted cancer cell elimination, and cellular medicinal delivery [55].

The US Food and Drug Administration (FDA) has approved magnetic nanoparticles of iron oxide, also known as magnetite or Fe3O4, for use in medication administration and clinical imaging [56]. Magnetic resonance imaging (MRI) can be utilized for observing iron oxide nanoparticles due to their magnetic nature, which thus allows for MRI-based imaging purposes [57]. Furthermore, magnetic iron oxide nanoparticles are used for temperature-triggered medication release because they produce heat while exposed to a magnetic field [58].

The hollow, ordered carbon graphitic nanostructures known as carbon nanotubes (CNTs) have a wide range of properties, such as a large aspect ratio, an extensive surface, and a lower weight [59]. These tubes typically have half of a fullerene structure capped at both ends, and their diameter can vary from 1 to 100 nm. CNTs are inert and chemically stable materials [60]. Carbon nanotubes (CNTs) seem to have a more dynamic biological applicability compared to conventional nanomaterials [61]. CNTs are site-specific and release the medication in a regulated manner. Their hollow tube form allows them to load a large amount of medications, and they can also boost the effectiveness of therapeutic compounds [62]. Mesoporous silica nanoparticles (MSNs) have emerged as a potentially effective and innovative medication delivery system because of their distinct mesoporous structure, which maintains a certain degree of chemical

stability, surface activity, and biocompatibility, and targeted medication administration of diverse pharmacological compounds [63]. Silica-based mesoporous nanoparticles are more resilient to external factors, including mechanical stress and deterioration, because of their strong Si-O connection [64]. The distinct advantage of MSNs is their well-defined surface characteristics, which facilitate the functionalization of the silanol-containing surface and manage drug loading and release [65].

Dendrimer

Dendrimers have become a significant class of nanostructured carriers for innovation in nanomedicine as a means of treating different diseases [66]. Dendrimers are formed from branched monomer units by selecting alternative building or branching units and surface functional groups. This allows for customization of the dendrimer's dimensions, flexibility, density, and solubility [67]. Additionally, they may include organic molecules and polymers in their structure, giving them unique chemical and physical characteristics [68]. Dendrimers, and PAMAM dendrimers, exhibit certain advantages over conventional linear polymers. These advantages include a well-defined composition with good monodispersity near proteins, an abundance of terminal functional groups, extensively branched inner cavities, ease of surface modification, and non-immunogenicity [69]. Consequently, because of their compelling benefits, dendrimers have been widely used in the field of biomedicine, particularly in cancer nanomedicine. In order to transport pharmaceuticals or genes, PAMAM dendrimers have been utilized as a platform to load various therapeutic medications and/or diagnostic agents [70].

Polymeric micelles

Polymeric micelles are multicompartment micelles that have a single hydrophilic shell around several compartments inside their hydrophobic core [71]. These are nanoscale structures that self-assemble in a micellar arrangement above the critical micelle concentration (CMC), often ranging in size from 10 to 200 nm [72]. Polymeric micelles are becoming increasingly attractive as drug delivery vehicles because they offer advantages over free drugs, in vivo pharmacokinetics, enhanced solubility, and the potential stability of their drug payload [73]. Polymeric micelles can have their size controlled such that they are sufficiently large to prevent premature clearance from fast glomerular filtration, which prolongs the duration of circulation

[74]. The properties of the polymeric micelles can facilitate an alternative mechanism of endosomal incorporation and improve the drug-loaded micelles' cellular localization [75].

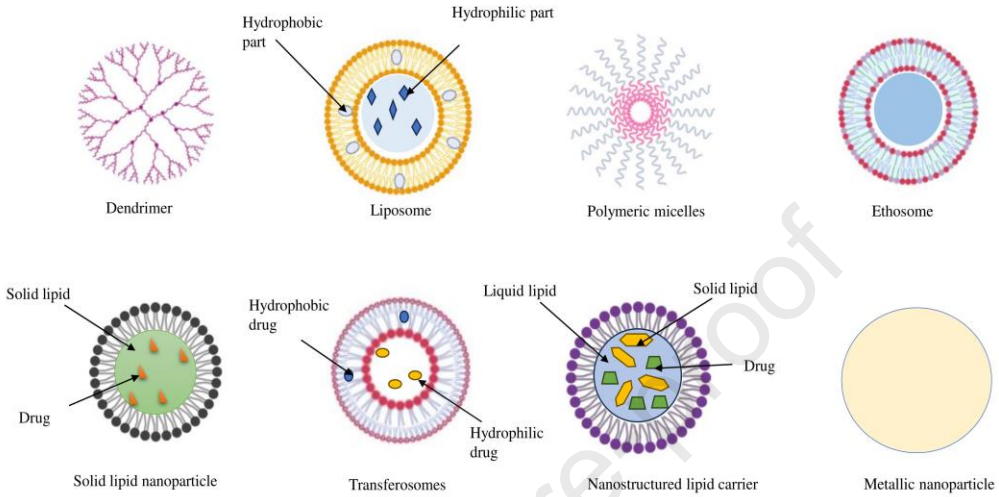


Figure 1. Various types of nanocarriers

Nanostructured lipid carrier

Recently, there has been a lot of interest in lipid nanoparticles, particularly solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLC) [76]. Solid lipid is used alone to manufacture SLNs, it forms a crystal lattice with minimal space for the therapeutics [77]. Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) are advanced lipid-based drug delivery systems designed to improve the bioavailability and stability of lipophilic drugs. While they share similar functions, their structures differ. SLNs consist of solid lipids, which form a stable matrix that encapsulates drugs, offering controlled release and protection from degradation. In contrast, NLCs, as a second-generation lipid nanoparticle, incorporate both solid and liquid lipids. This structural difference enhances drug loading capacity and provides greater stability compared to SLNs. Nanostructured lipid carriers (NLCs) offer notable advantages in drug delivery but encounter several limitations. While NLCs enhance drug solubility, some drugs, like quercetin, face issues with low percutaneous permeability and bioavailability,

impacting their effectiveness. Additionally, NLC formulations can become unstable over time, leading to phase separation or precipitation, which affects their clinical reliability. In dermatological applications, although NLCs aim to reduce skin irritation, they may not fully address the issue, potentially causing adverse reactions. For cancer treatment, NLCs improve drug targeting and reduce side effects compared to traditional methods, but their non-specificity can still harm healthy cells. In wound healing, NLCs enhance drug delivery to wound sites, yet environmental factors can compromise their effectiveness by affecting drug release profiles. Despite these challenges, ongoing research aims to refine NLC formulations to address these limitations and enhance therapeutic outcomes [78].

In NLC, a portion of the solid lipid is substituted with oil, producing an irregularly ordered lipid matrix that improves drug loading and prevents the drug from leaching out while being stored [79]. Similarly, NLC provide more stability since they prevent solid lipids from recrystallizing, maintaining the size essentially constant throughout storage [80]. The binary mixture of liquid lipid (oil) and solid lipid (solid) that makes up NLCs is a hybrid carrier with an average size of 10-500 nm. A long chain of liquid and lipid with a ratio of 99.9: 0.1 and a short chain of solid and lipid with a ratio of 70:30 make up the mixture of NLCs [81]. The benefits of SLNs are also present in NLCs, such as reduced toxicity, biodegradation, medication safety, gradual release, and the avoidance of organic solvents during manufacture [82]. In comparison to SLN, NLC formulation was found to be a more appropriate lipid carrier based on factors such as drug loading, percentage entrapment efficiency, and drug penetration into skin [83]. Compared to emulsions, NLCs' solid matrix allows them to effectively immobilize medicines and prevent the particles from aggregating [84]. NLCs have been thoroughly investigated as drug delivery vehicles for both hydrophilic and hydrophobic substances. NLCs can have benefits from both their lymphatic absorption and their ability to avoid first pass metabolism, more drugs will reach the site of action in order to prove their therapeutic value. The drug's entrapment in the lipid matrix also contributes to sustained drug release by delaying drug release, lowering dosage frequency, and enhancing patient compliance [85]. NLCs' small size ensures that they make direct contact with the skin and enhances the amount of medication that penetrates the skin [86]. By applying NLC gel topically, the skin forms a monolayered lipid film that has the occlusive effect of preventing trans-epidermal water loss (TEWL), increasing skin moisture content, and maintaining skin hydration [87].

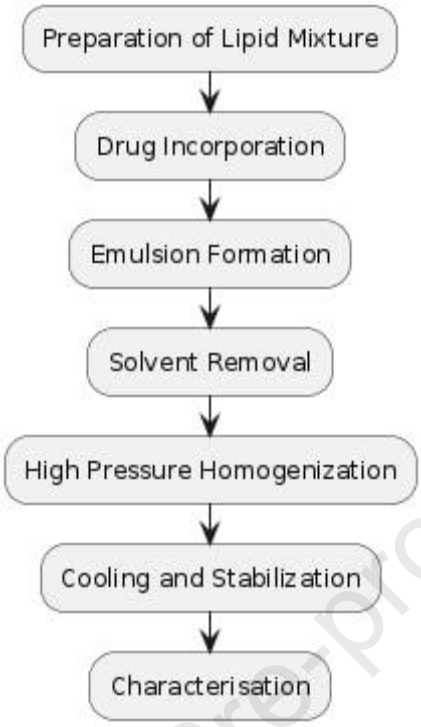


Figure 2: Key Steps in NLC Preparation Methods

Composition of NLC

NLCs are made up of various liquid lipids, solid lipids, and surfactants combined in particular ratios and distributed throughout aqueous solutions. It is important to choose biodegradable, non-toxic components for NLCs that hold therapeutic drug molecules and can be distributed throughout the body [88]. In NLC, a solid lipid replaces a significant amount of the oil component of the O/W emulsion, resulting in a solid particle matrix of this carrier system at the human body's temperature [89]. Liquid lipids (oils) are combined with solid lipids (ideally in a ratio of 70:30 to 99.9:0.1) to create combinations for the particle matrix [90].

Lipids

The primary component of NLC, lipid, influences the composition's stability, drug loading capability, and prolonged release characteristics [91]. A range of lipid compounds, such as fatty acids, glycerides, and waxes, constitute the basis for lipid nanoparticle dispersions [80]. It's crucial to carefully choose the right lipids before using them to prepare lipid nanoparticle dispersions [92]. The drug's solubility in the lipid has been suggested as a useful criterion for

choosing a suitable lipid, despite the lack of specific standards. The solid lipids that are most frequently used to prepare NLC include cetyl palmitate, stearic acid, glyceryl monostearate/monostearin, glyceryl behenate, and glyceryl palmitostearate [93]. Although the two most commonly utilized liquid lipids are oleic acid and caprylic/capric triglycerides, although to a lesser degree, canola stearin and myristyl myristate have also been utilized [94].

Emulsifiers

The substances known as surfactants are adsorbed at surfaces and lower interfacial tension [95]. Surfactants lower the surface tension or interfacial tension as well as the surface or interfacial free energy between the two phases [96]. The choice of surfactants for NLCs is dependent on several criteria, such as the NLC administration route and the surfactant's HLB value [95]. According to certain studies, the stabilizing substance affects the particles' crystalline form and controls a variety of factors, including their electrokinetic behavior [97]. NLC can be stabilized by causing steric and electrostatic repulsion within the particles.

The most frequently used non-ionic stabilizing agents are Tyloxapol, Tween® 20, and Poloxamer® 188, although soy or egg lecithins seem to be the preferred amphoteric compound stabilizing agents in the majority of studies [98]. Catalytic lipid nanoparticle production has also been done using quaternary ammonium surfactants. Furthermore, polyvinyl alcohol (PVA) is often chosen as a substitute stabilizer [99].

Type of NLC

NLC systems should efficiently transform inputs to preserve essential information with minimal energy. They need to be robust and adaptable to various inputs while meeting strict output standards. Iterative development is crucial for refining designs, and managing complexity through simplifications is essential as functionality increases. NLC can be divided into three types based on the differences in lipid and oil mixture composition as well as the different methods of production. NLC type 1 (imperfect type) (b) NLC type 2 (multiple type) (c) NLC type 3 is the amorphous type (c) NLC type 3 is the amorphous type (figure 3) [100].

NLC type 1

The imperfect form of NLCs contains glycerides and other lipids derived from fatty acids [101]. By adding more structural imperfections, such as by combining glycerides with different hydrocarbon chain lengths and saturations, the drug loading can be increased [102]. Moreover, their concentration of solid lipid is higher than that of liquid lipid [103]. Lipids that are spatially dissimilar can be mixed to create type I NLCs. The drug molecules embed in amorphous clusters and additional disordered crystals in molecular form [90].

NLC type 2

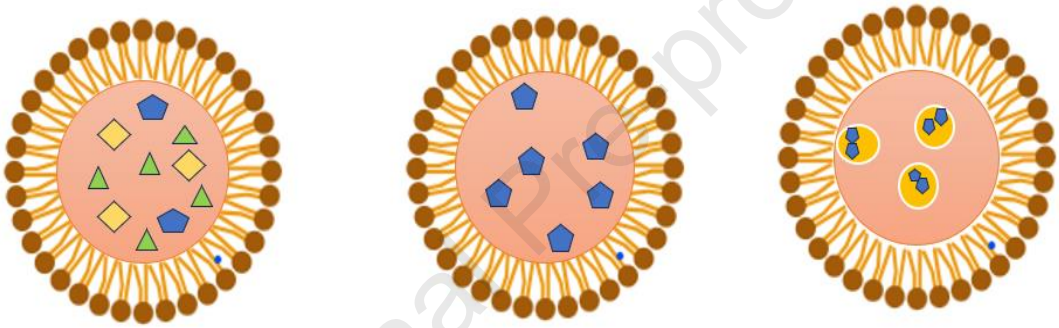
The amorphous form of NLCs is made up of solid lipids combined with a particular lipid, such as isopropyl myristate, or medium-chain triglycerides, like miglyol [100]. This has a lower crystalline structure and can stop the loaded drugs from leaking. Nevertheless, introducing a mixture of lipids stops the production of crystals throughout the cooling process [104]. Oil dissolves in type II NLCs more easily than solid lipids [105]. Type II NLCs contain substantial amounts of oil mixed with solid lipids due to the oil molecule's ability to easily penetrate into the lipid matrix at a low concentration of oil [81]. When more oil is injected than is necessary for its solubility, different phases may separate, which ultimately results in the formation of tiny, oily nanocompartments that are enclosed by the solid lipid matrix [95].

NLC type 3

Since they have a high liquid lipid concentration, the multiple types of NLCs improve both drug loading and dissolution. They are made up of different liquid lipid compartments that are dispersed throughout the solid core matrix [106]. Because the oil compartments are shielded by the solid lipid matrix and have a larger liquid lipid concentration, multiple-type NLCs provide longer release [107]. In this way, the drug is highly dissolved in a number of nanosized liquid oils that are part of the solid lipid matrix. Consequently, there is an increase in drug encapsulation. Furthermore, because the small oil droplets are contained in a solid lipid matrix, the drug is released with regulated release behavior, and drug leakage is less noticeable [108]. This is multiple type and was produced using the idea of w/o/w emulsion. This type of NLC is essentially oil-in-solid or fat-in-water, and it can only be produced using the phase separation

approach. This method can be used to formulate NLCs with a medication that exhibits greater oil solubility in order to enhance drug loading capacity and stability [109].

NLCs offer several advantages over traditional drug delivery systems, such as liposomes, solid lipid nanoparticles, polymer-based nanoparticles, and micelles. Compared to liposomes, NLCs are more stable, have better encapsulation efficiency, and are less toxic. Compared to SLNs, NLCs have higher drug loading capacity and improved drug release kinetics. Compared to polymer-based nanoparticles, NLCs are generally less toxic and more biocompatible. Compared to micelles, NLCs have higher drug loading capacity and better stability [108,109].



Type 1 Type 2 Type 3

Figure 3. Different types of NLC

Topical mechanism of action of NLCs

The rate of drug release is often influenced by a number of factors, including the solubility of the drug, the desorption of the drug that is surface bound or adsorbed, the drug's diffusion through the nanoparticle matrix, the erosion or degradation of the nanoparticle matrix, and the combination of the erosion and diffusion processes [110]. Therefore, the solubility, diffusion, and biodegradation of the matrix components control the release process. When the particles are delivered, an impulse can also cause this kind of release. The highly unordered lipid structures

present in NLCs are the cause of the increased drug loading. NLCs of specific structures can be triggered this way [82]. For a large enough drug load, the formation of a less organized solid lipid matrix is desired. Generally, drugs can be found in imperfections (e.g., amorphous) as well as in the spaces between lipid layers and fatty acids. When lipids are spatially quite similar to more or less highly organized matrix molecules, particularly when tristearin or other mono-acid highly purified glycerides are utilized, the drug load is extremely low, and medication excretion happens in a few days or hours. The rate of drug release from nanoparticles is influenced by factors such as drug solubility, surface desorption, diffusion, and matrix degradation. Nanostructured Lipid Carriers (NLCs) enhance drug loading due to their disordered lipid structures, which create spaces for drug incorporation. This structure allows for a more controlled and sustained release. Conversely, highly organized lipid matrices, like those using purified glycerides, result in lower drug loading and quicker release, typically within a few days or hours. [111].

Method of preparation of NLC (Table 1)

High pressure homogenization

This approach creates a drug-dispersed lipid melt by heating the liquid and solid lipid mixture over the solid lipid's melting point and adding drugs. Separately, the aqueous phase is made by mixing enough surfactant with deionized water and heating at the same temperature. These two phases are combined and quickly heated to an increased temperature using high shear homogenization to obtain the pre-emulsion. The pre-emulsion is immediately processed through the HPH-4 cycle at different pressures, after that, while stirring, the emulsion is cooled to room temperature [90]. The formulation of the adapalene NLC was accomplished with the use of three different types of surfactants: Plantacare, Ceremophore RH 40, and Tegocare, and Precirol ATO solid lipid combined with liquid Myritol lipid. Adapalene NLC was characterized by the following parameters: particle size 90–300 nm, index polydispersion <0.5, zeta potential -20 mV to -60 mV, efficient entrapment 84–98%, and morphological evaluation (spherical shape) as determined by transmission electron microscopy [112]. Red ginger extract-loaded nanostructured lipid carriers could successfully produce particles smaller than 200 nm. The polydispersity index of RG-NLCs varied from 0.104 to 0.172, with an average particle size ranging from 131 to 154 nm. The RG-NLC's zeta potential ranged from -33.00 ± 1.57 to -46.53 ± 0.38 mV; entrapment

efficiency was greater than 98%; and spherical particles were observed by transmission electron microscopy [113]. NLC was successfully produced utilizing a combination of palm oil (RPO), palm stem, and Tween 80 surfactant. The most effective formula Based on its small particle size, high RPO content, and surfactant concentration, RPO-NLC was selected with a particle size of 44.9 nm and entrapment efficiency of 99.9±0.02%. Red ginger extract NLCs achieved particles under 200 nm and over 98% entrapment efficiency, while palm oil-based NLCs showed the smallest particle size of 44.9 nm and a high entrapment efficiency of 99.9% [114].

Melt-emulsification and ultrasonication method

Drug lipids are combined and dissolved at a temperature higher than the solid lipid's melting point. At the same temperature as the lipid melts, the surfactant is dissolved in distilled water. After adding the aqueous phase to the lipid phase, the pre-emulsion is homogenized at high shear. Subsequently, this emulsion is ultrasonicated for a specific period of time. To obtain NLCs, this is solidified by cooling them to room temperature [115]. Curcumin-loaded NLC-optimized formulation showed a particle size of 121.8 nm, which is within the permissible range for brain delivery and is, expected to increase cell permeability when administered intranasally. The curcumin-loaded NLC PDI and zeta potential were observed as 0.201 ± 0.00 and 17.2 ± 2.35 mV, respectively. In addition, they discovered a stronger drug release profile with an initial burst and subsequent sustained release of 92.73%, as well as a higher entrapment efficiency of 92.74% [116]. Emulsification-sonication techniques were used to create a NLC that included imatinib. The formulations were characterized in terms of loading capacity, PDI, zeta potential, and particle size. The results showed that the formulations were 96.63 ± 1.87 nm, 0.27 ± 0.15, 96.49 ± 1.46%, and −32.7 ± 2.48 mV, respectively [117]. Quercetin and resveratrol co-loaded NLC-optimized formulations had a particle size of 191 nm, a polydispersity index (PDI) of 0.33, a zeta potential (ZP) of -10.00 mV, and an entrapment efficiency (EE) of 92.85% (quercetin) and 89.05% (resveratrol), respectively. Using the A431 skin cancer cell line, the combination's effectiveness was evaluated in terms of its cytotoxicity and anti-metastatic potential [86].

Solvent-emulsification evaporation method

In this procedure, the drug and the lipid are dissolved in a water-immiscible organic solvent (cyclohexane, chloroform). The resulting mixture is distributed into an emulsifier-aqueous

solution to create an o/w emulsion. The solvent is removed from the emulsion through evaporation under reduced pressure. The dispersion of nanoparticles in the aqueous phase is accomplished by evaporation [84]. Shirazi et al. develop SN38-loaded NLC against glioblastoma using the solvent emulsification evaporation method. NLCs were produced with a PDI of 0.25 and a particle size of 140 nm. Its entrapment efficiency was 81%, and its loading efficiency was 9.5% on average. NLCs were significantly more lethal to the U87MG human glioma cell line compared to the free medication, according to the results of the MTT test [118]. Dai et al. develop oridonin-loaded nanostructured lipid carriers as a controlled-release drug delivery system using the emulsion evaporation method. For all produced formulations, the narrow polydispersity index was less than 0.4 and the mean particle size was approximately 200 nm. The zeta potential range of around -35 mV to -50 mV indicated satisfactory physical stability for all formulations. Its entrapment efficiency was 74.25%, and its loading efficiency was 3.55%. These results showed the potential use of nanostructured lipid carriers as a drug delivery method with enhanced drug entrapment effectiveness and controlled drug release [119]. Aldawsari et al. develop ribociclib-loaded nanostructured lipid carriers against skin cancer. The solvent evaporation method was used to create RCB-NLCs, and Box-Behnken Design (BBD) was used to optimize composition. The constructed NLCs had a %EE of 86.07, a PDI of 0.242, and an average PS of 79.29 nm. The TEM investigation revealed that the NLCs are non-aggregative and have a spherical shape. The cumulative drug release from an in-vitro release study was 84.97 ± 3.37 % in 24 hours, which was much more than that from the RCB suspension (RCB-SUS). In both in vivo and biochemical studies, the modified NLCs produced positive results and improved the release properties of RCB. Based on the combined results, the encapsulation of RCB into NLCs appears to be a potential technique for the management of skin cancer [120]. Sartaj et al. develop a ribociclib-loaded nanostructured lipid carrier prepared by solvent evaporation followed by the probe sonication method. The Box-Behnken design response surface method was used to optimize the NLC formulation. The mean particle size of the prepared NLCs was 114:23 nm, the mean polydispersity index was 0:649, and the high entrapment efficiency was 87.7%. TEM images showed a homogeneous distribution and size. Due to the lipid utilized in the formulation, the in vitro permeation investigation indicated an increase in the level of penetration of the NLC formulation in comparison to a drug suspension. The solvent evaporation method produced SN38-loaded NLCs with a particle size of 140 nm and 81% entrapment efficiency, oridonin-

loaded NLCs with a particle size of 200 nm and 74.25% entrapment efficiency, and ribociclib-loaded NLCs with an average particle size of 79.29 nm and 86.07% entrapment efficiency, all showing enhanced drug delivery and stability [121].

Solvent-emulsification diffusion method

Lipids and drugs are dissolved in a solvent that has been saturated with water. A homogenizer emulsifies a solvent-containing medication and lipid mixture to create an o/w emulsion. After being diluted with excess water, the organic solvent diffuses from the emulsion droplets to the continuous phase, causing the lipid nanoparticles to precipitate. Using lyophilization or ultrafiltration, the solvent can be eliminated [107]. Aslam et al. develop nanostructured lipid carriers for enhanced transdermal delivery of glibenclamide. For the optimized glibenclamide-loaded NLC, the values for particle size, polydispersity index, zeta potential, entrapment efficiency, and drug loading were 120.687 nm, 0.217, −31.0 mV, 80.75 %, and 12.70 %, respectively. Due to greater penetration through rat skin, an in vivo pharmacokinetic investigation of the improved formulation demonstrated a considerable increase in bioavailability (1.36 times) when compared to the oral formulation of glibenclamide [122]. Iqbal et al. develop silymarin-loaded nanostructured lipid carrier gel and determine the antiproliferative, antioxidant, anti-inflammatory, and antitumor activities. Applying silymarin topically in the form of NLC gel significantly improves its potential to protect skin from UVB-induced damage, according to the findings of both in vivo and ex vivo experiments [87]. β-carotene-loaded nanostructured lipid carriers (NLC) were prepared using the solvent diffusion method. This research showed that NLC with very small particles and great retention of beta-carotene may be produced and used as suitable carriers of beta-carotene in meals. Therefore, β-carotene bioavailability can be increased while it is preserved within the lipid nanoparticles during storage. Glibenclamide-loaded NLCs enhanced bioavailability by 1.36 times, silymarin NLC gels improved UVB skin protection, and β-carotene NLCs increased bioavailability and retention [123].

Microemulsion method

Firstly, the liquid lipid is heated alone. Subsequently, melted solid lipid is added. Finally, the mixture is combined, and the medicine is added. Water and a surfactant are used to create the aqueous phase. The aqueous and lipid phases are both heated to high temperatures.

Subsequently, the lipid phase is introduced into the aqueous phase while the solution is kept at the same high temperature with mechanical stirring. Following the production of the micro-emulsion, it is constantly stirred and added to cold water, which dilutes it and facilitates the formation of NLCs [124]. Jain et al. develop and optimize artemether-loaded NLC (ARM-NLC) for intranasal delivery using a central composite design. The microemulsion method was utilized to manufacture ARM-NLC a novel intravenous formulation of β-artemether, which has been shown to be a superior alternative to the conventional artesunate formulation (C-AST) in treating malaria. This formulation utilizes nanostructured lipid carriers (NLC) to enhance drug delivery and efficacy, which resulted in an optimum formulation with a particle size of 123.4 nm and a zeta potential of 34.4 mV. The results reveal that NLC exhibited superior brain targeting efficiency in comparison to drug solutions. ARM-NLC demonstrated the highest drug targeting efficiency and drug transport percentage, with values of 278.16 and 64.02, respectively [125]. A PIO-loaded NLC or Pioglitazone-loaded nanostructured lipid carriers, represent an innovative drug delivery system designed to enhance the bioavailability and therapeutic efficacy of poorly soluble drugs, this formulation was successfully produced and optimized using the Box-Behnken design. The optimized nanoformulation exhibits a ZP of 14.9 mV and a PS of 211.4 nm. The results showed that the EE and PDI were, respectively, 70.18 and 0.257. There has been a sustained release of PIO from the NLC, according to the in-vitro drug release analysis. It was discovered that the formulation considerably increased PIO's permeability into the nasal mucosa in vivo. The drug's concentration entering the brain in vivo has greatly improved due to direct nose-to-brain transfer, which was seen from the IN-NLC. As a result, this research showed how useful IN-NLC is for utilizing PIO in AD therapy [126]. Curcumin-NLC produced by microemulsion-ultrasonication was characterized, optimized, and tested for release and digestion in simulated gastric medium (SGM). The outcomes indicated that 41% of the curcumin was released from NLC in SGM up to 2 hours. The DSC and XRD analyses revealed that curcumin was mostly confined in the NLC, which is related to its amorphous nature [127].

Table 1. Preparation methods of NLC

Method of preparation	Particle size	Zeta potential	PDI	Entrapment efficiency	Reference
High pressure homogenization	90-300 nm	-20 mV to -60 mV	<0.5	84-98 %	[112]
	131-154 nm	-33 mV to -46 mV	0.104-0.172	98 %	[113]
	44.9 nm	-	-	99.9 %	[114]
Melt-emulsification and ultrasonication method	121.8 nm	17.2 mV	0.201	92.74 %	[115]
	96.63 nm	-32.7 mV	0.27	-	[117]
	191 nm	-10 mV	0.33	92.85 % & 89.05 %	[86]
Solvent-emulsification evaporation method	140 nm	-15 mV to -20 mV	0.25	81 %	[118]
	200 nm	-35 mV to -50 mV	0.4	74.25 %	[119]
	79.29 nm	-	0.242	86.07 %	[120]
	114.23 nm	-	0.649	87.7 %	[121]
Solvent-emulsification diffusion method	120.687 nm	-31.0 mV	0.217	80.75 %	[122]
	451.4 nm	-50.4 mV	0.345	69.95 %	[128]
	189.4 nm	-20.8 mV	0.2	72 %	[129]

Microemulsion method	123.4 nm	-34.4 mV	-	-	[125]
	211.4 nm	14.9 mV	0.257	70.18 %	[126]
	24.73 nm	-7.43 mV	0.06	99.57 %	[130]

NLC in the management of different disease (table 2)

NLC for skin cancer

Skin cancer is a major issue for public health. It is often acknowledged that skin cancer is the most prevalent type of cancer that strikes humans, especially in the Caucasian community [131]. Approximately 3 million new instances of non-melanoma skin cancer (NMSC) are reported worldwide each year, with a predicted doubling in over 30 years. NMSC is more prevalent than melanoma [132]. Surgery and invasive therapies are the most often used approaches in the treatment of many forms of skin cancer, including melanoma [133]. Research has advanced quickly in recent years, leading to the identification of innovative medications and delivery systems that serve as effective substitutes [134].

Aldawsari et al. develop and optimize ribociclib-loaded nanostructured lipid carriers for skin cancer. In an effort to overcome the intrinsic bioavailability limitations, current research is focused on specifically creating and assessing nanostructured lipidic carriers (NLCs) for the topical administration of the chemotherapy medication ribociclib (RCB). With an emphasis on PS, PDI, zeta potential, and EE, the prepared NLCs were optimized. Studies on the release of RCB in vitro showed that NLCs could release the compound under control for up to 24 hours. Ex-vivo experiments demonstrated a considerable increase in the skin's retention capacity of the substance when compared to a typical gel formulation [120].

Iqbal et al. develop silymarin-loaded nanostructured lipid carrier gel for the treatment of skin cancer. The goal of the investigation carried out was to investigate the silymarin-nanostructured lipid carrier (NLC) gel's antiproliferative, antioxidant, anti-inflammatory, and anticancer properties. Antiproliferative activity, antioxidant activity, and anti-inflammatory activity results from in vivo and ex vivo investigations showed that topically applied silymarin in the form of NLC gel significantly increased its potential to protect skin from UVB-induced skin damage.

Results of an anticancer investigation using an albino mouse skin cancer model showed that mice given silymarin-NLC gel had superior tumor burden prevention [87].

Iqubal et al. developed, optimized, and evaluated a combinatorial NLC gel containing 5-fluorouracil and resveratrol to improve skin permeability across the epidermis and dermis layers and have a synergistic effect against skin cancer. According to in vitro efficacy research, linogel outperformed traditional formulations in terms of efficacy, having the lowest IC50 on the A431 cell line. As a result, this formulation may be able to treat skin cancer more effectively than the traditional formulation without having any negative side effects [135].

Moura et al. develop docetaxel and lidocaine-co-loaded NLC in the treatment of melanoma. This study presents a formulation of NLCDTX with analgesic and anti-tumor activity in a xanthan-chitosan hydrogel containing lidocaine (LDC). The hydrogel's intrinsic viscoelastic qualities were disclosed by a rheological study and the optimized nanoparticles contained 96% DTX. Cell viability tests indicated that once DTX was encapsulated in the hybrid formulation, its cytotoxicity decreased due to the prolonged release of the drug. These findings support the hypothesis that docetaxel loaded by NLC combined with lidocaine-in-hydrogel may represent a viable and alternate biocompatible formulation for the treatment of melanoma. The findings also showed intriguing analgesic and anticancer benefits of lidocaine for the treatment of melanoma [136].

Imran et al. formulate and optimize quercetin and resveratrol-co-loaded NLC gel for the treatment of skin cancer. Particle size, ZP, and entrapment effectiveness of the produced formulation were optimized via CCRD design. Skin irritation and permeability tests were used to assess the appropriateness of the produced gel. Dermatokinetic investigations established improved drug deposition in the epidermal layer. With regard to better skin cancer treatment, the produced formulation demonstrated the function of both the NLC and an incorporated medicine [86].

Venancio et al. develop topotecan (TPT)-loaded NLC for topical treatment of skin cancer. To summarize, this research revealed that the addition of TPT-NLC to hydrogels led to a considerable increase in skin penetration when compared to the formulations that contained free TPT. Lower doses of TPT (the IC_{50} of TPT-NLC is smaller than the IC_{50} of TPT) were used to

increase cytotoxicity in vitro against melanoma cells. The most promising method for the topical treatment of skin malignancies among all studied formulations was hydrogel containing dispersed TPT-loaded NLC [137].

NLC for Alzheimer's disease

Alzheimer's disease (AD) is a progressive, multifactorial, neurodegenerative, and chronic brain disease. It has been described as the primary cause of dementia globally [138]. AD constitutes a public health issue because the typically recommended drugs only address the symptoms of AD and do not stop the disease's increasing pathology [139]. The clinical manifestation of AD is marked by the presence of intracellular tau protein and extracellular amyloid plaques, which are caused by deposits of amyloid beta (Aβ) and neurofibrillary tangles (NFTs), respectively. These lesions resulted in neural cell death, which is reflected in memory impairment [140,141]

Donepezil hydrochloride (DPL) and embelin (EMB)-loaded NLC have been designed and improved to yield the intended therapeutic effect, regulated release, safer nasal delivery, efficient neuronal and cell uptake, and suitable drug loading. Studies using cell lines established a synergistic approach to medication combinations. The results of ex vivo permeation showed that improved NLCs more effectively penetrated the goat nasal mucosa. Studies on nasal histopathology showed no evidence of intercellular gaps or erosion for optimized NLCs, suggesting that DPL-EMB NLCs can be safely administered intranasally [142].

Jojo et al. develop and optimize pioglitazone (PIO's)-loaded nanolipid carriers for repurposing in Alzheimer's disease (AD). The aim of this work was to develop and optimize PIO's intranasal (IN) nanolipid carriers (NLC) for targeted brain delivery. The formulation was found to considerably increase PIO ex vivo's nasal permeability. Studies on toxicity were conducted to verify the formulation's safety for in vivo administration. Direct drug transport from the nose to the brain has been demonstrated in an in vivo biodistribution study conducted in rats [126].

Malvajerd et al. develop curcumin-loaded nanostructured lipid carriers to treat Alzheimer's disease. In this work, curcumin was loaded onto nanostructured lipid carriers (NLCs) in an attempt to increase its efficacy in treating Aβ-induced cognitive deficits in a rat model of AD. Reductions in oxidative stress markers in the hippocampal tissue and enhancements in spatial memory verified the efficacious role of NLCs for curcumin transport to the brain. The outcome

of examining the neuroprotective potential of Cur-NLC in both pre-treatment and treatment modes demonstrated that loading curcumin into NLCs is an effective approach for enhancing brain curcumin delivery and decreasing neurological abnormalities and memory impairments caused by AD [143].

Shehata et al. develop AST-loaded nanostructured lipid carriers. The purpose of this work was to produce and assess AST-loaded nanostructured lipid carriers (NLCs) for improved drug delivery from the nose to the brain, thereby increasing the therapeutic efficacy of the medication in a rat model of AD. As a result of its poor oral bioavailability, these results imply that intranasal delivery of AST in NLCs represents a potentially effective treatment for AD [144].

NLC for Parkinson's disease

Parkinson's disease (PD) is a neurological disease that affects 7–10 million individuals globally [145]. It occurs due to disruption to the brain's small regions responsible for movement, balance, and posture. Parkinson's disease (PD) is a frequent age-related neurodegenerative disorder that is identified by a decrease in dopamine due to the loss of dopaminergic neurons in the ventral part of the substantia nigrapars compacta [146].

A probe sonication method was used to create an entacapone-loaded nanostructured lipid carrier, which was then optimized using a QbD methodology. A prolonged release pattern of Entacapone from NLC was seen in the in vitro release pattern. By increasing the AUC in the plasma drug concentration profile, the orally delivered Entacapone NLCs demonstrated improved bioavailability, according to the in vivo pharmacokinetic data. so it concludes that the developing Entacapone NLCs may be an effective approach for enhancing the pharmacological bioactivity and oral bioavailability of the poorly soluble drug [147].

Dudhipala and Gorre prepare and characterize the pharmacokinetic (PK) and pharmacodynamic (PCD) activity of hydrogel-containing Ropinirole (RP)-loaded solid lipid nanoparticles and nanostructured lipid carriers for enhanced oral and topical distribution. PK investigations verified the enhanced transdermal and oral bioavailabilities resulting from hydrogel formulations and lipid nanoparticles, respectively. In comparison to control formulations, PK tests revealed 2.1 and 2.7-fold increases from oral administration of RP-SLN and RP-NLC and 3.0 and 3.3-fold enhancements from topical administration of RP-SLN-C and RP-NLC-C. Consequently, the

outcomes showed that SLN, NLC, and SLN and NLC-enhanced hydrogel formulations were taken into consideration as other methods and routes for the oral administration of RP for Parkinsonism. Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) offer significant advantages over conventional drug formulations. They enhance the bioavailability of drugs like Ropinirole (RP) by improving absorption and stability. In comparison to conventional formulations, SLNs and NLCs provide 2-3 fold increases in oral and transdermal bioavailability, as they protect the drug from degradation and ensure controlled, sustained release. Additionally, these advanced carriers allow for better drug targeting and crossing of biological barriers, making them more effective for delivering therapeutic agents like RP for Parkinson's disease [148].

Mishra et al. develop and characterize selegiline hydrochloride-loaded nanolipid carriers for the management of Parkinson’s disease. The drug-loaded NLC formulation that was optimized has demonstrated an entrapment efficiency of 93% and a loading capacity of 51%. The improved NLC formulation has demonstrated 70% release in 10 hours, and after that, the medication is released for up to 22 hours at a rate of up to 97%. A popular approach to treating Parkinson's disease (PD) is the use of nanolipid carrier (NLC) therapies, which improve the therapeutic efficacy of neurotherapeutics and allow for targeted administration [149].

Salunkhe et al. formulate and develop lipid-based nanostructured carriers (NLCs) containing idebenone (IDE) for delivery to the brain. Drug-loaded NLCs were developed using the nanoprecipitation process. The solid lipid Precirol ATO 5, oil Miglyol 840, and surfactant co-surfactant system made up of Tween 80 and Labrasol in IDE NLCs contribute to the drug's increased bioavailability by 2.8 and 4.6 times, respectively, in the brain compartment and plasma, compared to plain drug-loaded aqueous dispersion. Therefore, compared to conventional formulations, the IDE lipid-based nanostructured carrier system demonstrated the potential for drug administration and transport to the brain [150].

NLC for breast cancer

Breast cancer is a potentially lethal disease that continues to be a major global source of morbidity and mortality [151]. Globally, breast cancer is the most common cancer among women. Worldwide, it is predicted that more than 1.3 million new cases of breast cancer are

identified each year, with over 450,000 of those individuals expected to die from this disease [152]. According to the American Cancer Society, 268,670 new cases of breast cancer and 41,400 cancer deaths occurred in 2018 [153].

Nanostructured lipid carriers (NLCs) containing kaempferol (KAE) are designed to increase the cytotoxicity, effectiveness, and paclitaxel-dependent apoptosis of MDA-MB-468 breast cancer cells. Consequently, outcomes showed that paclitaxel, when combined with kaempferol-loaded NLCs, may enhance synergistic anticancer activity by suppressing apoptotic signaling, suppressing cancer cell cycle arrest in Sub G1 arrest, and decreasing the amounts of its anti-apoptotic Bcl-2 family genes. Considering all the data, adjuvant paclitaxel co-therapy with kaempferol-loaded NLCs can result in a more effective treatment for breast cancer [154].

To treat breast cancer, develop novel NLCs used as nanocarriers to deliver doxorubicin (DOX) and cisplatin (CDDP) simultaneously. In vitro, D-C-NLCs demonstrate the highest cytotoxicity when combined with two medications and tumor cells. The results of the in vivo investigation indicate that, in a breast cancer model, this formulation has the strongest anti-tumor effect. For the purpose of treating breast cancer, the built-in NLCs may be utilized to co-deliver CDDP and DOX. D-C-NLCs may be a potential nanomedicine for combinational and targeted therapy [155].

A NLC loaded with thymoquinone (TQ NLC) was developed to increase the cytotoxicity and bioavailability of TQ. The purpose of this study was to evaluate the cytotoxic effects of TQ-NLC on cervical cancer (HeLa and SiHa) and breast cancer (MCA-MB-231 and MCF-7) cell lines. TQ-NLC demonstrated dose-dependent antiproliferative activity against all cell lines, with MDA-MB-231 cells exhibiting the highest level of cytotoxicity. Moreover, TQ-NLC caused a cell cycle arrest. TQ-NLC was the material that affected MDA-MB-231 cells the most. It resulted in apoptosis and cell cycle arrest in the cells [156].

Poonia et al. develop and optimize a parenteral RSV formulation based on nanostructured lipid carriers (NLCs) for efficient delivery to breast cancer cells. The modified solvent injection approach was used to synthesize NLCs loaded with RSV (RSV-NLCs), which were then methodically refined utilizing a three-level-three-component Box-Behnken design. For the purpose of facilitating the efficient delivery of RSV to breast cancer cells, the RSV-FANLCs produced provided encouraging prospects with regard to solubility, sustained release, and

targeting potential. The result showed that RSV-FA-NLCs have the ability to target folate receptor-positive breast cancer cells [153]. Sabale & Jiwankar, 2024 studied that NLCs exhibit superior drug loading capabilities due to their unique lipid matrix structure, which allows for better encapsulation of hydrophobic drugs [157]. Patel et al., 2024 concluded in a study on doxepin that demonstrated NLCs significantly improved brain targeting efficiency, achieving a small particle size and high entrapment efficiency, thus enhancing therapeutic outcomes [158]. Moreover, Makkar et al., concluded that NLCs are designed to overcome the limitations of other colloidal carriers, providing a favorable release profile and improved physical stability [159].

Table 2. NLC for the management of different diseases

Drug	Excipient	Conclusion	Reference
Ribociclib	Labrafil, Labrasol, Campritol, Precirol, Gellucire, Stearic acid, Apifil, and Glycerol monostearate, Poloxamer and CremophorSpan-20, Span-60, Tween-20 and Tween-80	The NLCs were able to release RCB under control for up to 24 hours. Ex-vivo experiments shown a considerable increase in the skin's ability to retain the material compared to a conventional gel formulation. The encapsulation of RCB into NLCs appears to be a promising technique for the management of skin cancer.	[87]
Silymarin	Sefsol 218, Geleol, ethanol, Cremophor RH40, bile salt, carbopol 934, triethanolamine	Topically applied silymarin in the form of NLC gel significantly improves its capacity to protect skin from UVB-induced damage.	[87]

		The anticancer study's findings, which used an albino mouse skin cancer model as a paradigm, showed that animals given silymarin-NLC gel had superior tumor burden prevention.	
5-fluorouracil and Resveratrol	Labrasol, emulcire™ 61 WL 2659, Tween® 80, methanol, ethanol, acetonitrile, Carbopol 934, polyethylene glycol-400, triethanolamine	Exhibited better penetration profile and higher drug entrapment than the conventional formulation. Higher flux and permeability coefficient of optimized formulation demonstrated that the lipid-nanosystem crossed the barrier and reached into the epidermis and dermis layer of skin. The linogel exceeded the conventional formulation in an in vitro effectiveness testing, exhibiting the lowest IC_{50} on the A431 cell line.	[135]
Docetaxel and Lidocaine	Myristyl myristate, , Miglyol 812, chitosan, xanthan	Physical, biochemical, and histological metrics all demonstrated no adverse reactions from treatment with the hybrid hydrogel.	[136]

		A viable and alternative biocompatible formulation for the treatment of melanoma could involve docetaxel loaded by NLC combined with lidocaine-in-hydrogel.	
Quercetin and Resveratrol	Labrafil M 2125, Labrafil M 2130, Cremophor RH40, Carbopol 934, triethanolamine	Through their distinct molecular mechanisms of action, quercetin and resveratrol show synergistic effect and overcome drawbacks associated with using single medicines to treat skin cancer.	[86]
Topotecan	Stearic acid, oleic acid, lecithin, taurodeoxycholate, trehalose, chitosan, acetic acid, triethanolamine	In comparison to their respective formulations containing unloaded TPT, hydrogels containing TPT-NLC considerably enhanced skin permeability. Lower dosages of TPT were used to increase cytotoxicity in vitro against melanoma cells (the IC_{50} of TPT-NLC is lower than the IC_{50} of TPT).	[137]
Donepezil and Embelin	Stearic acid, Oleic acid, Black seed oil, Castor oil, Tween 80, Tween 20 Compritol 888 ATO,	Cell line research established a synergistic approach	[142]

	Precirol ATO5, Gelucire, Geleole, Thymoquinone, Capryol 90, Cremophore, Poloxamer 407	to drug combination. Ex vivo permeation showed that improved NLCs more effectively penetrated the goat nasal mucosa. The developed DPL and EMB-loaded NLC showed promising qualities and could be applied to intranasal AD treatment	
Pioglitazone	Tripalmitin, MCM, tween 80, pluronic F68, methanol, acetonitrile and ammonium acetate, Dimethyl sulphoxide	It was discovered that the formulation considerably increased PIO's permeability into the nasal mucosa. The safety of the produced formulation for in vivo administration has been established by a toxicity investigation. The IN-NLC showed direct nasal to brain drug transport, which greatly increased the medication's in vivo brain concentration. The current experiment illustrated the usefulness of IN-NLC for reusing PIO in AD management.	[126]
Curcumin	cetyl palmitate, Tween®80, Cholesterol	The effectiveness of curcumin's	[143]

		neuroprotective effects on an animal model of AD was examined, with a focus on its restricted size distribution (<120 nm) and high entrapment efficiency. Cur-NLC treatment of AD rats reduced the amount of amyloid plaques, thereby improving the disease's symptoms.	
Astaxanthin	Glyceryl palmitostearate, Poloxamer 188, Polysorbate 80, oleic acid, Methanol,	AST-NLCs delivered via nose-brain delivery to AD-like rats demonstrated anti-amyloidogenic, anti-cholinesterase, antioxidant, anti-neuroinflammatory, and anti-apoptotic effects.	[144]
Entacapone	Glycerol monostearate, Oleic acid, and Tween 80, Hydrogenated palm oil, Olive oil, ethanol, methanol, and trimethylamine	Orally administered Entacapone NLCs improved the AUC in the plasma drug concentration profile, indicating improved bioavailability. The nanoscale particle size, improved solubilization, inhibition of extensive metabolism, and	[147]

		increased efficiency, help in dosage reduction and improve overall therapy	
Ropinirole	Propylene glycol monocaprylate, tripalmitin, polyoxyethylene sorbitan monolaurate, EDTA, Poloxamer 188	In comparison to control formulations, PK tests revealed 2.1 and 2.7-fold increases from oral administration of RP-SLN and RP-NLC, and 3.0 and 3.3-fold enhancements from topical administration of RP-SLN-C and RP-NLC-C.	[148]
Selegiline	Stearylamine, tween 80, olive oil, Pluronic F68,	The produced formulation was found to have good loading capacity and entrapment efficiency Using a nasal delivery system to provide a selegiline HCl-loaded nanolipid carrier may have benefits for Parkinson's disease treatment.	[149]
Idebenone	Precirol ATO 5, Miglyol 840, methanol and 2-propanol, Tween 80 and Labrasol	IDE NLCs increase the drug's bioavailability by 4.6 times in plasma and 2.8 times in the brain compartment compared to ordinary drug-loaded aqueous dispersions. IDE lipid-based	[150]

		nanostructured carrier system evidenced the potential for drug delivery and transport to brain over the conventional formulations.	
Kaempferol	Compritol, Miglyol, poloxamer, chitosan oligosaccharides	An adjuvant paclitaxel co-therapy with kaempferol-loaded NLCs can result in a more effective treatment for breast cancer.	[154]
Doxorubicin and Cisplatin	Stearic acid, Precirol ATO, dimethyldioctadecylammonium bromide, triethylamine, soybean phosphatidylcholine, acetone, ethanol	In a breast cancer model, the in vivo study shows the highest anti-tumor activity The produced NLCs may be utilized to co-deliver CDDP and DOX as part of a treatment for breast cancer.	[155]
Thymoquinone	Olive oil, lecithin, phospholipid, Polysorbate 80	TQ-NLC demonstrated a high drug loading capacity and encapsulation efficiency. TQ-NLC has the potential to be developed into a drug for treatment of breast cancer	[156]
Resveratrol	stearic acid, oleic acid, folic acid, Poloxamer 188, Phospholipon 90 G	RSV-FANLCs provided encouraging prospects with regard to solubility, sustained release, and	[153]

		targeting potential.	

Conclusion

The use of nanoparticles for drug delivery is rapidly advancing, with lipid nanoparticles, including nanostructured lipid carriers (NLCs), playing a crucial role. NLCs offer numerous benefits and have a wide range of applications, making them a promising area for future development. While the high-pressure homogenization (HPH) technique is commonly used for NLC preparation (figure 2), challenges such as high operating temperatures, cavitation forces, and the need for diverse drug encapsulation have spurred the development of new lipid nanoparticle types and innovative preparation methods. This review highlights the potential of NLCs in treating various diseases, including skin cancer, Parkinson's, Alzheimer's, and breast cancer. NLCs have demonstrated effectiveness in both single and dual drug delivery systems, and no immunological activation was observed with the different excipients used. Future research should focus on addressing the current limitations of NLCs, optimizing preparation techniques, and exploring their full potential in a broader range of therapeutic applications.

Future perspectives

Looking ahead, nanostructured lipid carriers (NLCs) represent a promising frontier in drug delivery. Future research is likely to focus on enhancing their versatility and efficiency in encapsulating a wide range of therapeutic agents, including both hydrophilic and hydrophobic drugs. Advances in lipid composition and formulation techniques will aim to optimize drug loading capacity and stability, thereby improving shelf life and ensuring reliable performance. Precision medicine applications are expected to benefit from innovations in targeted delivery mechanisms, possibly integrating advanced surface modification strategies to enhance specificity and efficacy. Additionally, efforts will continue towards refining controlled release profiles to tailor drug release kinetics to specific therapeutic needs, minimizing side effects and improving patient compliance. As regulatory frameworks evolve to accommodate these advancements, the future of NLCs as a robust, versatile, and patient-friendly drug delivery system appears promising for addressing current healthcare challenges effectively.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: