REVIEW ARTICLE

NANOSTRUCTURED LIPID CARRIERS A COMPREHENSIVE REVIEW OF DESIGN, PREPARATION AND PHARMACEUTICAL APPLICATIONS.

AUTHORS: PADMA PREETHA J*, ATHULYA PK, HEMALATHA R, KIRUTHIKA V, LOKESH R, LOKESH S

CORRESPONDING AUTHOR

PADMA PREETHA J*
DEPARTMENT OF PHARMACEUTICS
KMCH COLLEGE OF PHARMACY
COIMBATORE

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Abstract

A New generation of lipid based nanoparticles called Nanostructured lipid carriers (NLCs) was developed to address the major shortcomings of solid lipid nanoparticles, particularly poor drug load, expulsion, and storage instability. NLCs are a binary mixture of solid lipid and liquid lipids, which forms a disordered lipid matrix, which permits greater drug entrapment efficiency and physical stability. This specially designed architecture facilitates the release of drugs in a controlled and sustained rate as well as allowing a very diverse range of lipophilic and moderately hydrophilic therapeutic agents. In this review, the basic ingredients of NLCs, such as lipid choice, surfactants, and how they impact on the particle stability and drug release profile are systematically summarized. The NLCs have a structural classification based on imperfect crystalline, amorphous, and multiple-type systems in relation to the discussion of drug loading and stability of storage. Preparation methods that are commonly used, like, high-pressure homogenization, ultrasonication, solvent-based, microemulsion, and double-emulsion are critically analyzed in terms of scalability, thermal stress, and limitations of formulations. Important parameters of characterization that control the behavior of NLCs such as the size of the particles, polydispersivity index, zeta potential, encapsulation efficiency, crystallinity, and in vitro drug release are brought to fore. Lastly, the review describes the general pharmaceutical uses of NLCs in oral, transdermal, nasal, ocular, parenteral, and brain routes of delivery with a focus on how NLCs may be used to improve the bioavailability and therapeutic efficacy.

Key Words Lipid nanoparticles, drug delivery systems, bioavailability enhancement, controlled drug release, nanostructured lipid carriers, and nanomedicine

Introduction

Solid lipid nanoparticles (SLNs) were produced as biocompatible drug carriers, although due to their highly ordered crystalline structure, the solids have a low drug loading and drug ejection. Nanostructured lipid carriers (NLCs), which are second-generation lipid nanoparticles, circumvent these limitations by using solid and liquid lipids to form a disordered matrix to enhanced drug encapsulation, stability, and controlled release[1]. Lipid nanoparticles offer biocompatibility, ability to encapsulate different medications, and controlled release with the methods of production influencing particle size, stability, and drug loading [2]. NLCs have been explored in the oral, topical, ophthalmic, pulmonary, and parenteral delivery; they inhibit the breakdown of drugs and can enable alternative patterns of release by diffusion [3]. To forecast performance and stability, characterisation (particle size, polydispersity index, zeta potential, morphology, encapsulation effectiveness and in vitro release) is necessary [4]. NLCs can enhance the pharmacokinetic properties, reduce side effects and facilitate future clinical use of the approach by targeting therapy, individualised medicine, and combination therapies [5].

Composition Of Nano Lipid Carriers

NLC also includes lipid liquid besides a solid lipid core that develops disorganized drug matrix, unlike SLN that has highly ordered lipid core. Besides stability issues which can ensue during long-term storage of SLN because of crystallization and expulsion of drugs, this disorganized nature allows loading more pharmaceuticals into the core, which is also solved by NLC. The ratio of solid to liquid lipid distorts the NLC core between 70: 30 to 99.9: 0.1. Since lipophilic molecules are more soluble in liquid lipid and lipid combinations cause defects, drug integration in these nanocarriers is more feasible[6].

Both solid lipid matrix and liquid lipids make up the second-generation lipid nanoparticles called nanostructured lipid carriers (NLC). NLC tend to have a size of between 200 and 400 nm. The NLC nanosizes depend on the different preparation methods. The upper nanosize range = 700 nm and above has been demonstrated to be less stable as flocculation and creaming continue. More concentrations of the surfactant are required to produe NLS particle sizes less than 200 nm but these are often undesirable in formulations. Nevertheless, NLC with a size of 100 nm tends to have problems due to recrystallization. But, due to their superior skin permeation, NLCs having a size of 100 nm are especially promising in some applications[7].

The stability, drug loading, and sustained release properties of the formulation are influenced by the lipid, which is the primary component of NLC. Most of these lipids are physiologically tolerated well, and were generally recognized as safe (GRAS), with cetyl palmitate being the exception. The right lipids should be selected before they are utilized to produce lipid nanoparticle dispersions. Although explicit recommendations have not been made, empirical evidence, including the ability of the drug to be dissolved in the lipid, has been proposed to be useful as a criterion to select an appropriate lipid. As an example, lipids having longer chains of fatty acids crystallize slowly compared to

lipids having shorter chains. Whereas, wax-based NLCs are more structurally stable, their more crystalline structure makes them exhibit significant drug ejection. To avoid these concerns with lipid crystallinity and polymorphism, two spatially distinct solid lipid matrices—a solid lipid and a liquid lipid/oil—were combined to create nanostructured lipid carriers (NLC)[8].

NLCs are created by dispersing various solid lipids, liquid lipids, and surfactants in aqueous solutions in precisely the right amounts. To be included in NLCs, drug molecules must be non-toxic, biocompatible, and appropriate for systemic distribution[10].

Solid Lipids

The combination of numerous chemical compounds that have melting points over 40°C. One can easily tolerate these solid lipids. It is biodegradable and acceptable to the human use. A few examples are beeswax, carnauba wax, dynasan, precifac, stearic acid, cutina CP 8 etc[8].

Liquid lipids

The two most commonly used liquid lipids are oleic acid and caprylic/capric triglycerides, but canola stearin and myristyl myristate are also occasionally used[9].

Surfactants

The surfactants employed in preparing the NLCs can be classified into three categories which are neutral, ionic and non-ionic. These surfactants accumulate in the Stern layer of the particle and prevents aggregation of the particles in the storage due to electrostatic repulsion of the same electric charges on the particles[6].

The surfactants decrease the surface tension or the interfacial tension as well as the free energy of the surface between the two phases. The HLB value of the surfactant and the method of administration are two factors that influence the kind of surfactants to be used in NLCs. According to some research, the stabilizing substance controls a number of aspects, including the particles' electrokinetic behavior and shapes their crystals. It is possible to stabilize NLC by increasing the electrostatic and steric repulsion of the particles. Tyloxapol and Tween 20 are the most widely used non-ionic compound stabilizing agents, despite the fact that soy or egg lecithin compounds appear to be the preferred amphoteric compound stabilizing agents in most studies. With the aid of quaternary ammonium, lipid nanoparticles have also been produced through catalysis[9].

Classification Of Nanostructured Lipid Carriers (NLCs)

NLCs can be classified into three types in terms of their lipid composition and structure: multiple type (Type III),amorphous type (Type II), and imperfect crystal type (Type I).These structural differences are calculated to be made to address the demerits of traditional solid lipid nanoparticles, especially maximum loading of drugs and loss of drugs during storage. Through the adjustment of lipid miscibility and NLCs also provide a better entrapment of drug, greater stability and better control over crystallinity, drug release behavior[11].

Type I

Imperfect Crystal Type. In a bid to make Type I NLCs also known as the imperfect crystal type, solid is mixed, fatty acid chains or other space arrangements of the lipids. This combination disrupts the common crystalline structure of the lipid matrix resulting in imperfections formations that cause the development of imperfections, and is capable of holding increased quantities of drug[1]. The comparatively low lipid order is found in such systems causes deformation of crystal lattice. The level of such imperfections may be modified through the choice of appropriate triglycerides or fatty acids. Lipophilic substances are more soluble in liquid lipids than in solid lipids and therefore, the increase in the percentage of liquid lipids leads to an increase in drug loading[6].

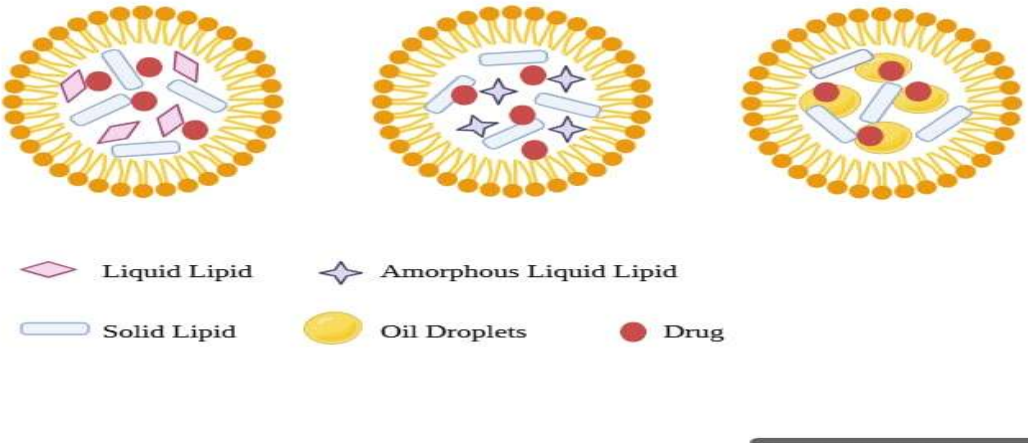
Type II

Amorphous Type. Type II NLCs are also those with solid but amorphous internal matrices. This amorphous nature is obtained through the mixture of solid lipids with the chosen oils, and this helps to avoid the formation of an extremely crystallized structure. Crystallization is a significant expulsive agent of drugs, therefore having an amorphous matrix is useful to prevent or greatly decrease drug leakage during storage[13]. These NLCs are usually prepared with solid lipids together with the lipids like isopropyl myristate, hydroxyoctacosanyl hydroxystearate, or medium-chain triglycerides like Miglyol® 812. These compositions provide moderate drug loading with minimum drug rejection[1]. Dibutyl adipate is also commonly utilized in Type II NLCs as it does not solidify during homogenization and cooling, and thus enhance formulation stability[1,13].

Type III

The multiple type, which is also referred to as type III NLCs, have a more complicated internal structure and are commonly characterized by the oil, fat, water (O/F/W) model. These are especially adapted to drugs that are more soluble in liquid lipids or oils than in solid lipids. They are usually prepared by the technique of phase separation where the drug is initially dissolved in small oil droplets and then it is dispersed within the lipid framework of the solid[1]. Type III formulations need a larger portion of oil as compared to other types of NLC. In a miscibility gap

between the solid lipid and the oil, a phase separation will take place in the matrix with high concentration of oil[13]. Oil nanocompartments were enclosed by a solid lipid shell enables drug release to be controlled and reduces leakage of drugs hence contributing to improved stability[12,13].



Preparation Methods Of NLC:

High-Pressure Homogenization (HPH)

High-pressure homogenization, which entails melting solid lipid and miking it with liquid lipid and medication to generate a homogenous lipid phase, is one of the most popular and successful techniques for producing NLCs. This molten lipid phase is dispersed throughout a heated aqueous surfactant solution to produce a pre-emulsion. The pre-emulsion is then passed through a high-pressure homogenizer, where severe shear and cavitation pressure break the droplets into nanoscale size .The nanoemulsion recrystallizes into solid NLCs with enhanced stability and drug loading after cooling [2]. By quickly freezing the drug-lipid melt, grinding it into microparticles, and homogenizing it in a cooled surfactant phase to reduce thermal degradation, cold HPH alters this procedure .Although the encapsulation of heat-sensitive or hydrophilic pharmaceuticals is improved by this cold technique, the particles produced are typically slightly bigger than those produced by hot HPH [14].

Ultrasonication Method

By applying high-frequency ultrasound to a heated lipid-surfactant pre-emulsion, ultrasonication produces severe cavitation that lowers droplet size.To create a coarse emulsion, the molten lipid blend (solid + liquid lipid + medicine) is first distributed in a heated aqueous surfactant solution [2].

After that, this emulsion is subjected to ultrasonic waves from a bath sonicator or probe, where droplets are broken into nanoscale dimensions by collapsing cavitation bubbles that apply high shear [14].The lipid droplets solidify into NLCs with particle sizes of between 30 and 180 nm when the sonicated nanoemulsion cools [2].The technique involves careful control of sonication time and amplitude to prevent overheating or foaming, and despite its ease of use and capacity to generate microscopic particles, it runs the danger of metal contamination via probe attrition [14].

Solvent-Based Methods

By dissolving solid and liquid lipids in an organic solvent that is either water-miscible or slightly water-miscible, solvent-based techniques create NLCs. When the lipid solution is combined with an aqueous surfactant phase, a nano emulsion is created. Rapid solvent migration into the aqueous phase during emulsification causes instantaneous lipid precipitation as nanoparticles and decreases lipid solubility[6] .When the organic solvent is volatile, the lipid matrix is further solidified by controlled evaporation under low pressure, producing homogenous NLCs without thermal stress on heat-sensitive drugs [15]. Because they don't require high-pressure equipment, these methods are particularly useful when pharmaceuticals degrade at high temperatures or when lipids cannot be melted [15]. However, in order to comply with safety and regulatory requirements, the method necessitates careful solvent selection and total elimination of remaining solvent [6].

Microemulsion Method

In order to create NLCs, a hot, thermodynamically stable microemulsion comprising molten solid lipid, liquid lipid, surfactant, and co-surfactant in a single transparent phase must first be created [15]. Lipid nanostructures precipitate and the clear microemulsion breaks down instantly when it is quickly distributed into cold water [15]. The abrupt reduction in temperature causes the lipid droplets to crystallize quickly, creating consistently sized NLCs [16]. The

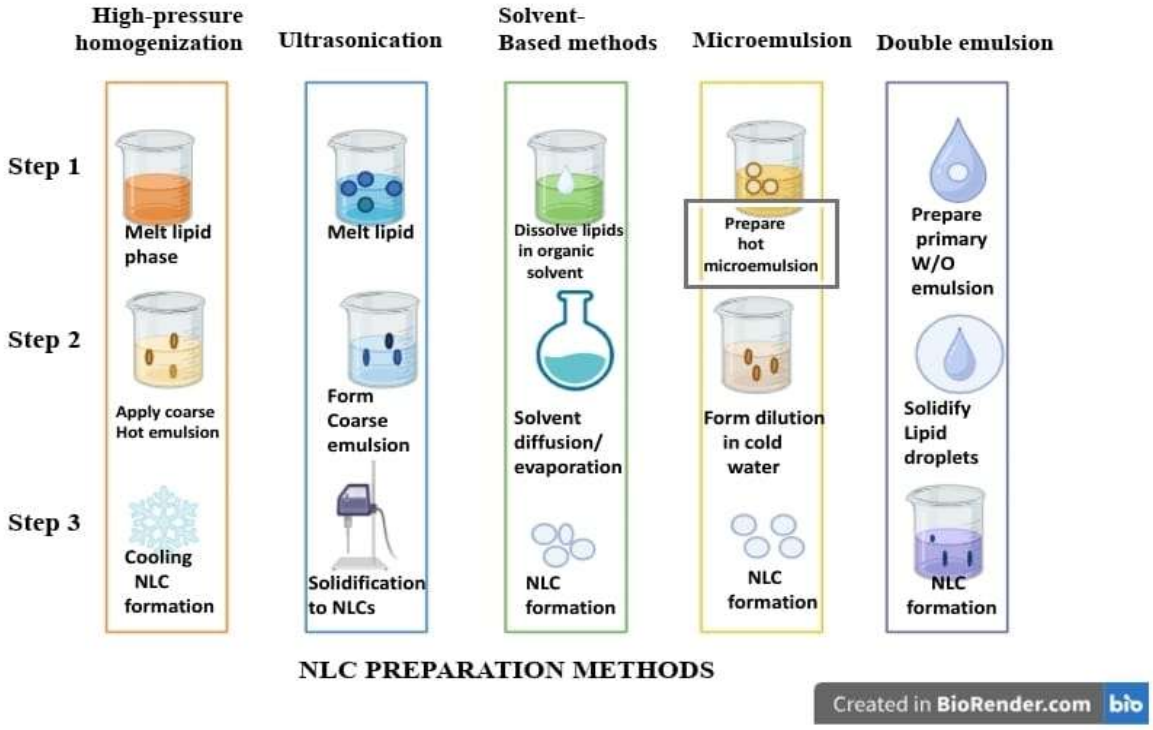
method is straightforward and appropriate for thermolabile chemicals because it doesn't require high-pressure or high-energy equipment [16].
However, after the cold-water quenching stage, it yields very diluted dispersions and requires high concentrations of surfactants and co-surfactants [15].

Double Emulsion (W/O/W) Method

By first creating a primary water-in-oil (W/O) emulsion and then spreading the aqueous drug solution inside a molten lipid phase by high-shear mixing, the double-emulsion method encapsulates hydrophilic pharamaceutical. This stabilizes the medication inside the inner aqueous droplets. The primary emulsion is added to an external aqueous surfactant solution to form a water-in-oil (W/O/W) double emulsion [17].
NLCs that effectively capture hydrophilic and peptide-based drugs are produced when lipid droplets solidify due to solvent evaporation or cooling in the lipid phase [18].
The method prevents drug diffusion into the exterior phase by optimizing the emulsifier content and viscosity of the internal and external aqueous compartments[18]. It is sensitive to osmotic pressure gradients, emulsification speed, and stability of the two aqueous phases, despite being perfect for delicate water-soluble actives [17].

Method	Key steps	Advantage	Limitations
High-Pressure Homogenization (HPH)	Lipid melting → hot pre-emulsion formation→ high-pressure homogenization→ chilling and → NLC formation.	Scalable, reproducible, produces uniform particle size	Heat exposure, costly equipment, unsuitable for thermolabile drugs
Ultrasonication	To solidify nanoparticles→ melt the lipid, → create a coarse emulsion, → sonicate the bath or probe, → and then cool.	Simple, low energy, small particle size	Metal contamination risk, overheating, small batch capacity
Solvent-Based Methods	Dissolve lipids in organic solvent; → combine with an aqueous surfactant → allow solvent to diffuse and evaporate → then precipitate the lipids.	Suitable for heat-sensitive drugs, no high-pressure equipment	Residual solvent concerns, regulatory issues, slow solvent removal
Microemulsion Method	Create a heated, → transparent microemulsion, → quickly disperse it in cold water, and → then immediately precipitate or crystallize it → produce NLC.	No high-energy devices, good for thermolabile compounds	Requires high surfactant/co-surfactant levels, forms dilute dispersions
Double Emulsion (W/O/W)	Make the water in oil primary emulsion, → disseminate it into the external aqueous phase, → solidify the lipid droplets→ then obtain NLCs.	Ideal for hydrophilic and peptide drugs, good retention	Highly sensitive process, drug leakage risk, low emulsion stability

Table 1:



Mechanism Of Drug Release Of NLCs

The release of drugs through Nanostructured Lipid Carriers (NLCs) is primarily based on the composition and operated through processes such as matrix erosion, diffusion, or particle uptake. NLCs consist of an unorganised lipid matrix of liquid lipids which enables high concentration of drugs and limits drug release. The drug may be incorporated into fatty acids, lipid layers or amorphous lipid regions. In comparison to better-structured lipid matrices (i.e., purified glycerides such as tristearin), NLCs allow release times of hours to days owing to their structural defects.

The most important parameters that influence drug release of NLCs are:

1.Diffusion: The diffusion of drug molecules slowly through the lipid matrix is possible because they are insoluble in lipids, which makes them be released at a controlled rate.

2.Matrix erosion: The lipid matrix decays or erodes with time due to the penetration of water, enzymatic activity, or hydrolysis and releases the drug.

3.Partitioning and solubility: Partitioning of the drug to the lipid matrix affects the rate of release with a high lipid affinity reducing the rate of release and increased aqueous solubility increasing the rate of release.

4.Lipid mobility: The higher the mobility of lipids, the higher is the permeability of the matrix and the faster the release of the drugs.

5.Surfactants and cosurfactants: These anti-agents alter the lipid structure, which influences the kinetics of drug loading and release.

6.Particle size: Minuscule NLCs have a higher surface area-volume ratio, which usually has faster release of the drug.

7. PH and ionic strength: Environment changes may destabilize the matrix and change the partition of drugs and affect release.

8.External stimuli: NLCs that react to stimuli such as temperature, light, or magnetic fields to regulate drug delivery.

9.Targeting ligands: Surface ligands enhance targeted delivery to cells or tissues affecting localized drug delivery.

In general, the dynamics of NLC drug release is a multifactorial phenomenon because of the lipid content, drug therapy properties, particle features, and environmental stimuli, which enables the tailorable release profiles of various therapies[19].

CHARACTERIZATION OF NLC

1.Particle Size

The stability of NLCs is of great importance to particle size and distribution. Narrow size distribution results in smaller size which decreases aggregation, increases physical stability as well as storage behavior. Surface area is also controlled by particle size and this affects solubility, biocompatibility and release of drugs. NLCs typically range from 10–1000 nm[20]. DSL measures particle size as the hydrodynamic diameter, and it depends on the lipid composition, the concentration of surfactant and the process parameters like homogenization and sonication[22].

2.Polydispersity Index

PDI quantifies consistency of particles size with 0 (monodisperse) to 1 (heterogeneous). When the PDI is less than 0.3, the dispersion is homogeneous and stable enough to administer drugs on a regular basis[22].

3. Morphology

SEM and TEM are used to determine morphological characteristics. SEM identifies the spherical particles of smooth surfaces and not aggregated[22]. TEM analysis, which was conducted following negative staining with 1 percent phosphotungstic acid and at 80 kV, offers finer details on the shape of the particle and nanostructured core[21].

4. Encapsulation Effectiveness (EE)

The extent of encapsulation is indirectly calculated by quantifying free drug in the aqueous phase with the help of ultrafiltration (Amicon Ultra, MWCO 3 kDa). EE is calculated using:

EE (%) = (A2 − A1) / A2 × 100,

A1 is the free drug and A2 the total drug content[21].

5. Zeta Potential / Surface Charge

Surface charge is observed through Zeta potential and it predicts colloidal stability based on electrostatic interactions[24]. Stable dispersions will have ZP with the value above 30 mV. In the case of lipid nanoparticles, the presence of stability is denoted by a value above -60mV of SLNs and above -30mV of NLCs[25]. The measurements are done at a temperature of 25 C by a zeta potential analyzer which is equipped with a 90 o helium neon laser[23].

6. Drug Release in Vitro

In vitro release experiments are an indicator of in vivo performance of NLCs. The dialysis procedure is the most widespread one in which drug-loaded NLCs are incubated in release medium at 37 o C, and sampled at regular times[20]. Release kinetics are analyzed using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models[22]. Other methods are dialysis sac variants, Franz diffusion cell and USP dissolution apparatus[24].

7. Degree of Crystallinity

The measure of crystallinity is done by DSC and XRD[26]. It is dependent on drug loading, storage, and formulation viscosity. Defects in the lattice of solid lipids increase entrapment and stability of drugs[20]. XRD can also give the information about crystalline phases, lattice parameters, and the size of the grains, whereas the SAXS can be used to conduct supramolecular analysis of lipid nanoaggregates[26].

Route Of Administration of NLCs

1. Oral Route

Oral drug delivery is plagued with significant obstacles such as high rate of hepatic first-pass metabolism and low solubility of drugs, which leads to low bioavailability. A nanoparticle system and in particular chitosan-modified nanoparticles increase oral absorption. Nanostructured Lipid Carriers and Solid Lipid Nanoparticles have longer release, and they assist to maintain the constant plasma levels. Some of the main obstacles to oral delivery are P-glycoprotein efflux pumps, enzymatic or chemical degradation. Nanoparticles of lipids enhance lymphatic delivery which decreases first-pass metabolism. Indicatively, baicalin loaded NLCs prepared by emulsion-evaporation and low temperature solidification have been shown to be associated with high drug loading, and entrapment efficiency that results in significant increases in oral bioavailability[27].

2. Transdermal Route

Skin is a good method of local and prolonged drug delivery because it has a large and accessible surface with few side effects on the system. It is used as a protective layer, with the main layer being the outer Stratum Corneum, a compact layer that prevents the entry of large molecules (>500 Da). The absorption of drugs is through transepidermal route (through lipophilic intercellular lipids or corneocytes) or transappendageal route (through hair follicles and sweat glands). Lipophilic drug carriers such as deformable liposomes and more so Nanostructured Lipid Carriers (NLCs) have demonstrated superior skin penetration, prolonged release and minimal skin irritation over conventional liposomes. The NLCs enhance the stability of drugs, increase skin hydration and skin elasticity due to their occlusive ability, small sized particles and enhance entire skin penetration leading to extended therapeutic action. NLC-based topical preparations, although first investigated in cosmetics, have a great potential in enhancing dermal and transdermal drug delivery, with the assistance of penetration enhancements, and the advantage of quicker wound healing and reduced dosing schedule[6].

3. Nasal Route

By directly targeting the lung epithelium, avoiding first-pass metabolism, and lowering systemic toxicity and dosing frequency, inhalational drug delivery provides a non-invasive method of treating pulmonary disorders. Because of their greater diffusional mobility and bioadhesive lipophilic qualities, Nanostructured Lipid Carriers (NLCs) with particle sizes smaller than 500 nm improve deep lung deposition and prolong lung residence time. By avoiding macrophage clearance, particles smaller than 260 nm prolong therapeutic effects by releasing drugs under controlled conditions. Surfactants and co-solvents are frequently used in formulations to reduce lung inflammation. NLC-based pulmonary delivery is a promising approach to enhance drug availability, retention, and controlled release at the lung site. For instance, celecoxib-loaded NLCs (about 217 nm) showed high entrapment efficiency (90%), sustained drug release, and successful alveolar deposition in mice[28].

4. Ocular Route

Delivery of drug particularly to the posterior segment, is difficult due to the eye's special structure and protective barriers, which include the cornea, sclera, retina, blood-ocular barriers, tear turnover, and blinking. Although topical administration is recommended for the anterior segment, less than 5% of the drug reaches the posterior segment due to its short residence time and limited tissue penetration. NLCs have become an effective ocular delivery system by reducing risks that exist with invasive methods, like intravitreal injections, including vision loss and infection; through enhancement of corneal penetration by increasing the residence time owing to their mucoadhesive properties; and reducing bioavailability with less toxicity. NLCs have proven promising to treat various eye diseases including; inflammation, infections, glaucoma and posterior segment disorders due to the safety and efficacy of non-invasive drug delivery to the eye[29].

5. Brain Delivery

Delivering drugs to the brain is difficult due to the blood-brain barrier (BBB) and drug efflux mechanisms. Due to their size, high encapsulation of drugs and the ability to evade the reticuloendothelial system, nanoparticles like Solid Lipid Nanoparticles and Nanostructured Lipid Carriers can be used to target the brain. These lipid nanoparticles enable transcytosis by endothelial cells, enhance retention of drugs in the capillaries of the brain, and results in a concentration gradient that causes a tight junction to open to permit passage of the BBB. They are able to deliver both lipophilic and hydrophilic medications through several different delivery methods. The positively charged lipid nanoparticles enhance the accumulation of the drug in the brain tissue, whereas the choice of surfactants and in particular polysorbate 80 enhances the efficiency of the brain delivery[30].

6. Parenteral Route

Parenteral lipid carriers of submicron fat emulsions such as Intralipid and other parenteral lipid carrier products such as Diazemuls and Diprivan that had issues with the rapid drug release and degradation. Whereas liposomes enhanced the encapsulation of hydrophilic and lipophilic drugs that were released steadily and were less toxic, the liposomes had limitations because of their high cost, stability, complexity of manufacturing and scale-up challenges. Although polymeric nanoparticles offered surface modification and tunable release, they faced similar obstacles, and despite micro-particle depots, few nano-products were commercialized. The advantages of earlier systems were combined in solid lipid nanoparticles (SLNs; 100–400 nm): better stability, drug protection, sustained release, and simpler, less expensive scaling up. Lipid–drug conjugates allowed for hydrophilic drug delivery, while nanostructured lipid carriers improved drug loading/stability, primarily for dermal use with developing parenteral applications. For a variety of treatments, including Central nervous system and anticancer drugs, injectable lipid nanoparticles (SLN, NLC, and NLDs) enhance pharmacokinetics, targeting, and efficacy[31].

Applications of Nanostructured Lipid Carriers (NLCs)

1.Improvement of Bioavailability of Lipophilic Drugs

NLCs improve the bioavailability of lipophilic medicines that are poorly soluble in water. They are small (<100 nm), which enhances systemic circulation, surface area, drug solubilization, membrane contact, and absorption[22].

2.Oral Administration

NLCs have been reported to increase solubility, absorption, and gastrointestinal stability of poorly soluble drugs in the mouth. Their solid-liquid lipid matrix enables them to be drug loaded, release in controlled fashions and remain stable. Surface functional groups such as thiolation or PEgylation facilitate absorption into the intestines and through mucus[22].

3.Parenteral Delivery

Compared to conventional SLNs, the solid and liquid lipids in NLCs improve drug encapsulation, stability, and release. Anticancer drugs (e.g. paclitaxel), less toxic amphotericin B, diagnostic agents, antiarthritic, cardiovascular, and nucleic acids have been used as NLCs gene therapy[22].

4.Cosmetic Applications

NLCs bring high-penetration of the actives (vitamins, antioxidants, retinoids), increase absorption with an absence of irritation and decrease water loss, which contributes to hydration and collagen synthesis. They are applied in masks, serums and creams in customized cosmeceuticals[22].

5.Nose-to-Brain Targeting

Delivery of drug into the brain through olfactory and trigeminal routes goes through the NLCs and does not avoid the blood-brain barrier. Their size (100200nm)and flexibility on the surface enable the best absorption into the brain, lower side effects on the system and have potential in neurodegenerative disease treatment[22].

6.Ocular Drug Delivery

NLCs enhance the ocular bioavailability and pre-corneal retention of lipophilic drugs such as ibuprofen. Stearylamine and permeation enhancers (e.g., Transcutol IP, Gelucire 44/14) increase the corneal penetration and increase retention[27].

7.Chemotherapy

NLCs enhance the stability, efficiency and cytotoxicity of anticancer drugs and decrease adverse effects. They permit high drug loading, sustained release, drug chemical stabilization, and surmounts SLN's drawbacks, including medication leakage and low drug loading capacity[27].

8.Food Industry

Less developed, NLCs can be used to provide nutritional supplements (e.g. coenzyme Q10) in food and beverages, increasing physicochemical stability and bioavailability[27].

9.Alzheimer's Disease

Loaded with donepezil hydrochloride (DPL) and embelin (EMB), NLCs are the most effective drugs in Alzheimer treatment with controlled delivery, safe nasal administration, efficient cellular uptake, and drug loading[9].

10.Breast Cancer

NLCs supplemented with kaempferol (KAE) improve cytotoxicity, efficacy, and paclitaxel-induced MDA-MB-468 breast cancer cell apoptosis. NLCs based on dual drugs can co-deliver cisplatin (CDDP) and doxorubicin (DOX) in treating breast cancer[9].

Future Prospective

Nanostructured lipid carriers (NLCs) have several disadvantages despite their advantages, including restrictions on large-scale production, long term stability and residual solvent issues [33]. However, NLCs have shown considerable potential for targeted drug delivery and their enhanced drug loading capacity, stability, and undergo surface functionalisation with targeting ligands, which enables tissue-specific administration and reduces systemic toxicity [34].Thus, the primary focus of future research should be on process optimisation, green and scalable manufacturing methods, and the creation of standardised regulatory guidelines to facilitate clinical translation [33].Additionally, innovative formulation strategies such as surface modification, ligand-based targeting, and stimuli-responsive NLCs offer promising opportunities for precision medicine; however, additional in vivo testing and clinical translation in areas such as gene delivery, brain targeting, and cancer therapy will determine their true therapeutic impact [34].

Conclusion

Nanostructured lipid carriers represent a significant advancement over solid lipid nanoparticles by overcoming significant disadvantages like poor drug loading, crystallization-induced drug expulsion, and storage instability. The incorporation of liquid lipids into the solid lipid matrix creates structural defects that enhance encapsulation efficiency, controlled drug release, and stability. NLCs offer formulation flexibility, biocompatibility, and application in a variety of modes of administration, including oral, transdermal, nasal, ocular, parenteral, and brain delivery. Despite encouraging experimental results, large-scale production, long-term stability, and regulatory standardisation remain major challenges. Overcoming these limitations is the key prerequisite for enhancing the clinical viability and translation potential of NLC based drug delivery platforms.

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Competing Interest

The authors declare that there are no competing interests regarding the publication of this review article.

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