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Nanostructured Lipid Carriers (NLC): A Novel Drug Targeting Carrier System

Rohan Khutale[1*], Preeti Khulbe[1]

[1]Gyan Vihar School of Pharmacy, Suresh Gyan Vihar University, Jaipur, Rajasthan, India.

*Corresponding Author: Rohan Khutale

E-mail: khutale.rohan@gmail.com

ABSTRACT

Nanostructured lipid carriers (NLC) can overcome the limitations associated with traditional lipid-based carriers like Solid Lipid Nanoparticles (SLN). The solid and liquid lipids in the NLC system generate a nanostructured matrix that offers improved stability, controlled release, and drug loading capacity. The encapsulation of hydrophilic or lipophilic drugs within the NLC (nanostructured lipid carriers) increases the solubility and bioavailability of these compounds. In addition, because of NLCs and their prolonged action due to drug release, patients are more likely to follow their prescribed prescriptions. This article will guide you through the various forms of NLCs that can be prepared using different characterization techniques and offer specific advantages. It underscores their potential in many medicinal applications — such as for drug delivery into the mouth, the skin or the veins.

Key words: Nanostructured Lipid Carriers, Solid Lipid Nanoparticles, Drug Delivery System, Characterization, Preparation Methods, Bioequivalence, Stability, Biocompatibility.

INTRODUCTION:

Nanostructured Lipid Carriers (NLCs), a second-generation lipid-based nanocarrier platform, aim to overcome the drawbacks of conventional solid lipid nanoparticles (SLNs)[1]. These novel carriers are a combination of liquid and solid lipids stabilised by ethers which lead to the formation of a new imperfect crystalline structure. This configuration improves drug incorporation, stability, and release associated with storage [2]. The production of Natural lipid carriers (NLC) have attracted a significant interest in pharmaceutical and cosmeceutical industries as a consequence of their capacity to entrap both hydrophilic and lipophilic drugs [3]. The nanoscale dimension leads to better permeability and retention (EPR) effects thus targeted delivery and sustained drug release. In addition, the NLCs are used for the drugs that have short half-life due to like biocompatibility, reduced toxicity and protection from degradation [4]. NLCs have been investigated for uses in many other fields, such as drug delivery systems for oral, topical and parenteral administration [5]. They enhance bioavailability, enable controlled release profiles, and aid in the delivery of poorly-soluble drugs. Due to this potential and the adaptability of NLCs, they have become a favored system to address challenging issues in drug delivery and therapeutic design [6].

STRUCTURE OF NLC:

NLCs have better stability and stability over SLNs due to their unique structure [7]. There are three major types of NLCs depending on their structural differences:

TYPE I: IMPERFECT CRYSTAL TYPE:

Imperfect crystal is a special structural type of NLCs. This type is characterized by a matrix formed by a crystalline solid mixture of liquid and solid lipids with intrinsic defects. The regular crystal lattice is disrupted and defects created when the liquid lipids are added to the solid lipid matrix [8]. The system's capacity to incorporate and retain active pharmacological

ingredients (APIs) is enhanced by the voids generated by such faults in the matrix. Disrupting the crystalline structure of SLNs increases their drug-loading capability compared to conventional SLNs [9]. This reduces the possibility of storage-related premature release, an issue often seen in systems with complete crystallinity. Good for poorly soluble drugs, as lipid matrix on drug helps solubilize and disperse the drug [10]. This is quite useful for formulations that require excellent stability and high drug loading efficiency. This makes these NLCs ideal for preparing injectable, topical, or oral drug delivery systems for poorly soluble medications, enhancing both bioavailability and therapeutic outcome [11].

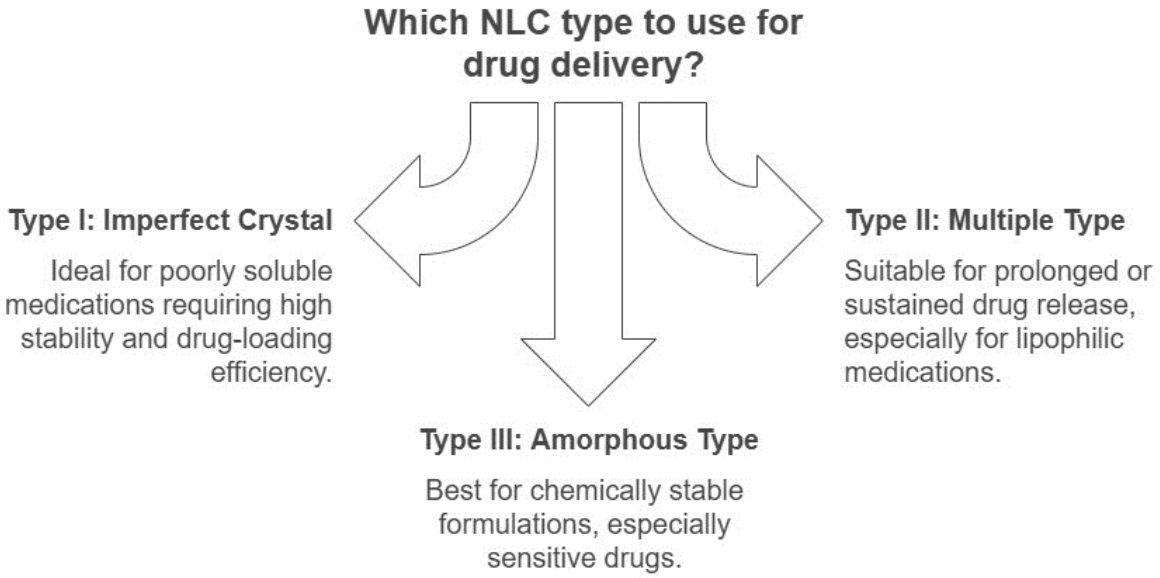
TYPE II: MULTIPLE TYPE:

Optimizing medication encapsulation and release patterns is the goal of the complex system known as Multiple Type of NLCs. Liquid lipids are distributed as microscopic Nano compartments throughout the solid lipid matrix [12]. These Nano compartments serve as reservoirs within the solid lipid, improving the drug's distribution and stabilization. By confining the medication inside the liquid lipid compartments, the structural design stops the medicine from being expelled. The therapeutic efficacy is enhanced by this design, which allows for controlled and prolonged drug release [13]. The stability of the medicine is maintained throughout storage by reducing the ejection caused by crystallization. Provides a degree of adaptability in regulating medication release rates in response to changes in the ratio of liquid to solid lipids. Works wonders for creating medication delivery systems that need prolonged or sustained drug release, like depot injections or topical formulations with a long-acting duration. To create new drug delivery systems that assure longer therapeutic activity and improved patient compliance, the adaptable platform provided by multiple-type NLCs can be used [14].

TYPE III: AMORPHOUS TYPE:

To overcome the difficulties of lipid crystallization in traditional systems, scientists developed an amorphous form of NLCs. These NLCs differ from others in that they include lipids in an

amorphous, rather than crystalline, form [15]. The lipid matrix stays disordered recognitions to the amorphous character, making it a more accommodating habitat for drug molecules. Phase separation and drug expulsion during storage are both prevented by the lack of crystallization. For medications that have a tendency to precipitate in crystalline lipid matrices, this property is very beneficial. The encapsulated medicine and carrier are both made more chemically stable by their amorphous nature. Provides enhanced stability for medications that are susceptible to degradation when subjected to the stress caused by crystallization. This is the perfect storage solution for medications that are sensitive to temperature changes



and do not form crystals [16]. It is commonly employed in formulations that priorities steady drug release and minimum degradation. It is appropriate for pharmaceuticals that require high chemical stability, like biologics, peptides, and other sensitive compounds. An innovative method for medication delivery, Amorphous Type NLC offers improved stability and adaptability for difficult therapeutic agents [17].

Figure.1 Types and application of NLC

DRUG RELEASE PATTERN FROM NLCS:

Drug release from NLCs occurs through various mechanisms depending on the formulation design, lipid composition, and drug properties. NLCs offer controlled, sustained, and targeted drug release profiles, enhancing the therapeutic efficacy of encapsulated drugs.

MECHANISMS OF DRUG RELEASE:

DIFFUSION-CONTROLLED RELEASE:

Through the surface of the nanoparticle, the medication diffuses out of the lipid matrix and into the surrounding media.As an example, concentration gradients may cause hydrophilic medications embedded in the lipid matrix to slowly diffuse out.
A topical gel based on NLC that delivers hydrophilic antifungal drugs, such as miconazole, is an example of a formulation [18].

EROSION-CONTROLLED RELEASE:

Drugs enclosed in lipid bilayers are released when the bilayers gradually degrade or wear away. Enzymatic or environmental factors frequently dictate this process.
Lipid degradation allows release from biodegradable NLCs, which allow for prolonged delivery of insulin. For example, in the treatment of diabetes, injectable NLC systems can have a lasting effect [19].

BURST RELEASE:

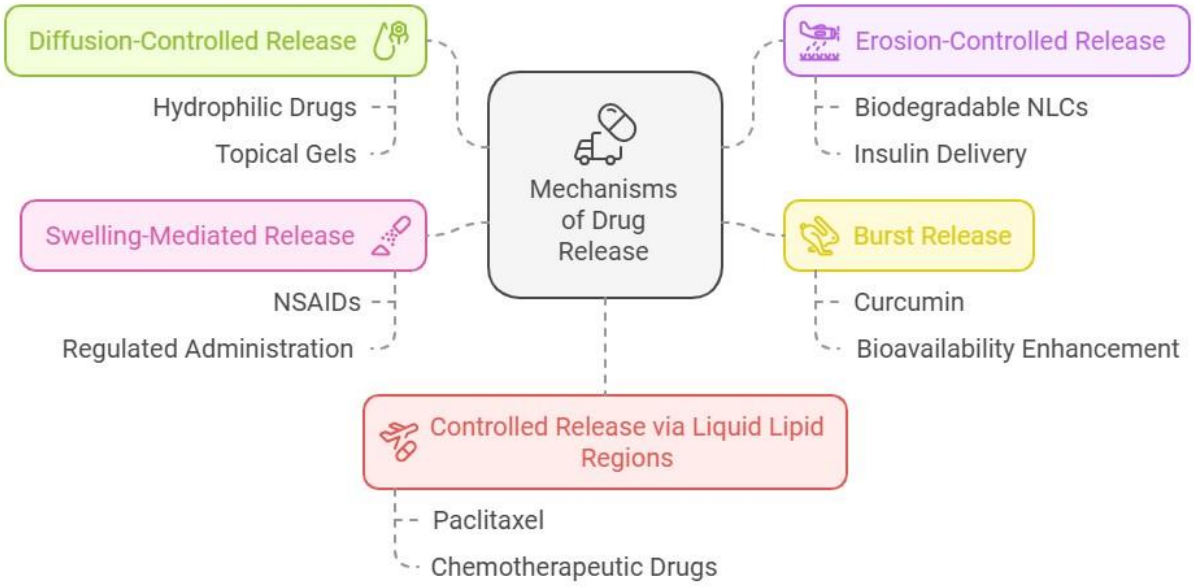
Medications that are either surface-adsorbed or loosely encapsulated on particles allow for rapid release. A more gradual, persistent release phase typically follows.
NLCs loaded with curcumin exhibit an early burst release, which enhances bioavailability. Skin benefits from marketed formulation Lipobelle^{TM} DN CoQ10, a topical product based on NLC [20].

SWELLING-MEDIATED RELEASE:

Because the lipid matrix swells when it absorbs water, medications are able to diffuse out more readily. NLCs are utilized for the regulated administration of NSAIDs, such as ibuprofen [21].

CONTROLLED RELEASE VIA LIQUID LIPID REGIONS:

Amorphous or liquid lipid areas in NLCs allow for slow drug release, which lessens the likelihood of ejection. NLCs loaded with paclitaxel for regulated administration of chemotherapeutic drugs [22]. The lipid-based marketed formulation for acne treatment



Epiduo® Gel combines adapalene and benzoyl peroxide. Atorvastatin NLC Gel for anti-inflammatory effects in cardiovascular diseases [23-24].

Figure 2. Mechanisms of Drug Release

ADVANTAGES OF NLCS:

An improved method of delivering drugs based on lipids is known as nanostructured lipid carriers, or NLCs [25]. Their design takes into account the advantages and disadvantages of SLNs. Peruse the benefits below:

ENHANCED DRUG LOADING CAPACITY:

The drug's accommodation space is increased by the combination of solid and liquid lipids in NLCs, which generates an incomplete lipid matrix [26]. Low drug loading is a common problem with SLNs because of their stiff crystalline structure, which might cause drug expulsion with time. Liquid lipid absorption into NLCs decreases crystallinity, enabling increased drug payloads. The ability to encapsulate a bigger lipid matrix is particularly helpful for medicines with low solubility, such as curcumin and paclitaxel [27].

IMPROVED STABILITY:

Drug expulsion during storage is prevented by the addition of liquid lipids, which break the crystalline arrangement. When compared to typical carriers, NLCs exhibit superior stability throughout a wide range of conditions, including temperature changes and extended storage [28].

Good for medications that have a tendency to precipitate or degrade in traditional lipid delivery systems. One example is the superior stability of vitamin E formulations in NLCs compared to SLNs [29].

CONTROLLED AND SUSTAINED RELEASE:

NLCs regulate the drug's diffusion and erosion from the lipid matrix, allowing for a regulated release of the medicine. Because of this property, NLCs are well-suited for long-term diseases like diabetes or cancer, where frequent dosage is not an option. By utilizing NLCs, sustained-release formulations of medications such as ibuprofen and clotrimazole have been created, guaranteeing that therapeutic levels remain constant throughout time [30-31].

IMPROVED BIOAVAILABILITY:

By improving their solubility in the lipid matrix, NLCs improve the bioavailability of hydrophobic medicines. The use of NLCs allows the encapsulated medications to be absorbed via many biological membranes, including those in the lungs, skin, and gastrointestinal system.

Because of their superior solubility and absorption, curcumin-loaded NLCs have a far higher oral bioavailability than free curcumin [32-33].

REDUCED TOXICITY AND BIOCOMPATIBILITY:

The potential for systemic toxicity is decreased by the fact that NLCs are made up of biocompatible lipids that exist naturally. Because of their biocompatibility, NLCs are ideal for delicate uses such as medication delivery through the skin, the eyes, and the mucosa [34]. In contrast to more traditional topical creams or gels, anti-inflammatory medications delivered via topical NLCs cause less skin irritation [35].

VERSATILE DRUG ENCAPSULATION:

Highly adaptable, NLCs are able to include a wide variety of medications thanks to their lipid matrix. Protecting pharmaceuticals from the environmental hazards of heat, light, and oxygen, NLCs prolong their shelf life [36]. Insulin and peptides are examples of thermolabile medications that are stabilized during storage and administration when they are encapsulated [37].

TARGETED DRUG DELIVERY:

Thanks to their microscopic size, NLCs are able to cross the blood-brain barrier and reach targeted tissues and cells more effectively, including tumors and brain tissue [38]. NLCs are well-suited for targeted cancer therapy due to their capacity to accumulate in tumor tissues, which results in an enhanced permeability and retention (EPR) effect. Enhanced drug targeting and reduced systemic toxicity are two benefits of doxorubicin and other chemotherapeutics formulated with NLC [39].

EASE OF SCALABILITY AND MANUFACTURING:

Scalable technologies like high-pressure homogenization and ultrasonication can be used to create NLCs, making their industrial manufacturing a realistic possibility. Other nanocarriers, such as liposomes or polymeric nanoparticles, can be more expensive, but the overall cost of lipids is reduced by their comparatively low cost and simple manufacturing techniques [40].

APPLICATIONS IN VARIOUS ROUTES OF ADMINISTRATION:

ORAL: If a medicine has a low solubility, taking it orally can increase its bioavailability. Nutritional supplement NLCs enriched with curcumin are one example [41].

TOPICAL: It improves the absorption of anti-aging or anti-inflammatory medications by the skin. Instance: NLC creams containing CoQ10 [42].

PARENTERAL: Allows for the gradual and controlled release of paclitaxel and other anticancer medications [43].

PULMONARY: It aids in the efficient administration of asthma medications like salbutamol or budesonide [44].

COMPONENT OF THE NLC:

Component	Role	Examples	Selection Criteria
Solid Lipids	Provide structural matrix for NLCs. - Control the release of the drug. Prevent rapid drug release.	Glycerylbehenate (Compritol® 888 ATO) Stearic acid - Palmitic acid - Cetyl alcohol - Triglycerides (e.g., tripalmitin)	Compatibility with the drug. Melting point higher than body temperature.
Liquid Lipids (Oils)	Disrupt crystalline structure of solid lipids. - Increase drug loading capacity. Improve solubility of lipophilic drugs.	Medium-chain triglycerides (MCTs) - Oleic acid - Isopropyl myristate - Squalene - Caprylic/capric triglycerides	Miscible with solid lipids. No phase separation or instability.
Emulsifying Agents	Stabilize lipid nanoparticles. Prevent aggregation. Improve dispersion in the medium.	Surfactants: Polysorbates (e.g., Tween 80), Sorbitan esters, Lecithin Co-surfactants: Sodium lauryl sulfate (SLS), Poloxamer 188 -	Non-toxicity and biocompatibility. Effective in stabilizing nanoparticles over prolonged storage.

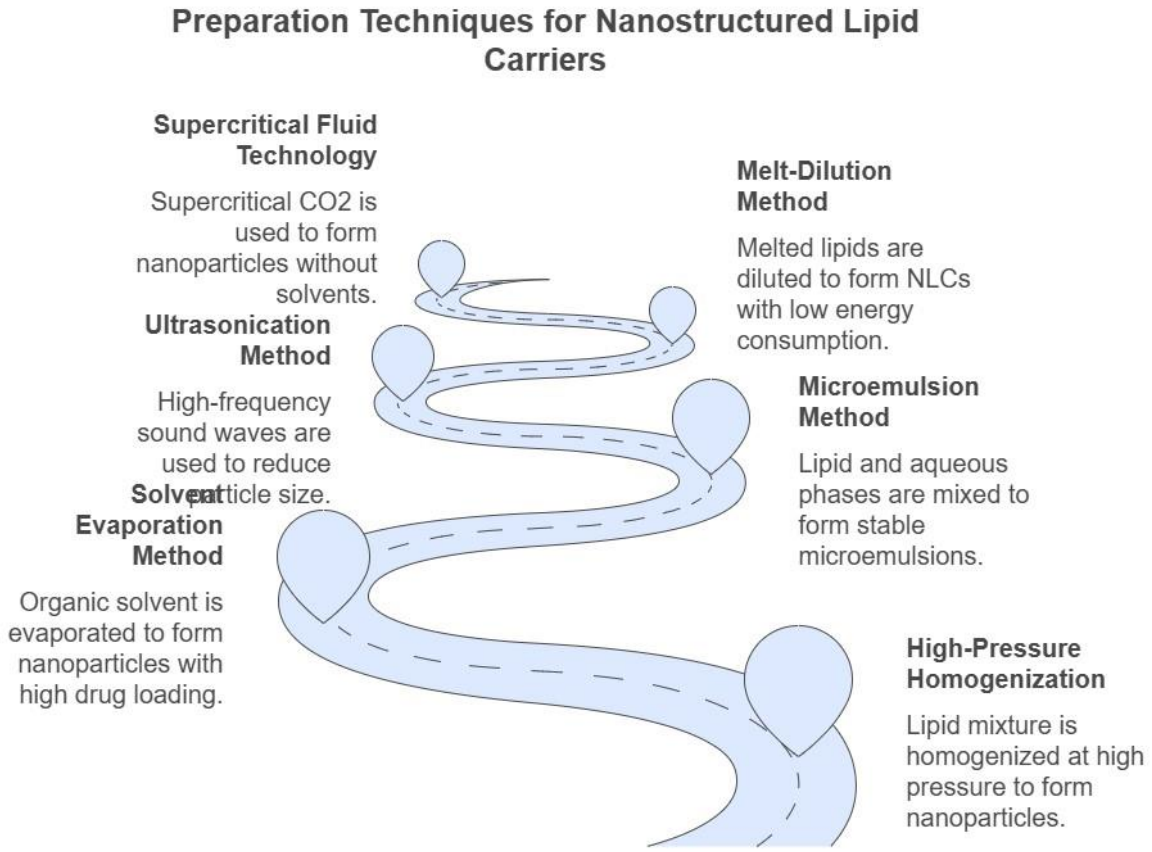
		Natural stabilizers: Chitosan, Gelatin	
Optional Additives	Protect NLCs during freeze-drying (Cryoprotectants). Prevent microbial growth (Preservatives). Stabilize lipids (Antioxidants).	Cryoprotectants: Trehalose, Mannitol - Preservatives: Benzyl alcohol Antioxidants: Tocopherols, Ascorbic acid	Compatibility with the NLC formulation. Ensure stability during processing and storage.

PREPARATION TECHNIQUES FOR NLCS:

NLCs can be prepared through several methods that allow for the optimization of drug loading, particle size, and stability. Below are the most commonly used preparation techniques [45]:

Preparation Method	**Mechanism**	**Advantages**	**Disadvantages**
High-Pressure Homogenization	Lipid mixture is homogenized under high pressure to form nanoparticles.	Scalable, reproducible, efficient, controlled particle size.	Requires high energy input.
Solvent Evaporation	Organic solvent used to dissolve lipids and drugs; solvent evaporates to form nanoparticles.	Simple, high drug loading, suitable for thermolabile drugs.	Use of organic solvents, solvent removal is required.
Microemulsion	Forms a microemulsion which is inverted to create NLCs.	High drug loading, stable, narrow size distribution.	Requires precise control of temperature and solvent conditions.
Ultrasonication	Lipid mixture is sonicated to form	Simple, quick, suitable for small	Limited scalability,

	nanoparticles.	scale, minimal surfactant use.	requires high energy.
Melt-Dilution	Lipid mixture is melted, mixed with drug, and diluted with water to form NLCs.	Simple, low energy consumption, suitable for thermolabile drugs.	Limited drug loading capacity compared to other methods.
Supercritical Fluid (SCF)	Supercritical CO2 used to dissolve and precipitate lipids and drugs into nanoparticles.	Solvent-free, environmentally friendly, precise control over particle size.	Requires specialized equipment, expensive.
Coacervation/Precipitation	Lipids and drugs precipitate out of a solvent, forming nanoparticles.	Simple, low energy, suitable for hydrophobic drugs.	Control over particle size can be challenging, requires careful solvent management.



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CHARACTERIZATION OF NLCS:

The characterization of NLCs is crucial to assess their size, morphology, drug-loading efficiency, release properties, stability, and biocompatibility. Below are the main characterization techniques used for NLCs [46]:

Technique	Purpose	Parameters Analyzed
Particle Size & Zeta Potential	To determine particle size, distribution, and stability	Size, PDI, Zeta potential
TEM/SEM	To examine morphology and internal/external structure	Size, shape, surface morphology
Drug Loading &	To determine the amount of drug encapsulated in the NLCs	Drug loading efficiency, encapsulation efficiency

Encapsulation		
DSC	To analyze the thermal behavior and drug-lipid interactions	Melting points, crystallinity, stability
XRD	To study the crystallinity and drug-lipid interaction	Crystallinity, phase changes
FTIR	To investigate molecular interactions between drug and lipid matrix	Functional group analysis, drug-lipid interactions
In-vitro Release	To assess the release profile of the encapsulated drug	Release rate, controlled/sustained release
Stability Studies	To evaluate physical, chemical, and microbiological stability	Aggregation, phase separation, sterility
Kinetic Modeling	To predict the release mechanism of the drug	Release kinetics, mechanism analysis (e.g., zero-order, Higuchi)

CONCLUSIONS:

There are several benefits of using NLCs instead of more conventional lipid-based carriers for medication delivery. The controlled release profile, increased stability, and increased drug loading capacity are all benefits of NLCs, which are made possible by merging solid and liquid lipids. Because of these characteristics, NLCs are useful in many drug delivery systems, such as those for targeted therapies, sustained release formulations, and medicines that are not very water-soluble. To optimize the formulation parameters, NLCs are characterized using a variety of methods, including drug encapsulation efficiency, zeta potential testing, and particle size analysis. In addition to being biocompatible and having minimal toxicity, NLCs have the capacity to encapsulate hydrophilic and lipophilic medications, which lends credence to their prospective use in clinical settings. The potential of NLCs to revolutionize drug delivery systems, boost treatment efficacy, and increase patient compliance is promising, and further study into their manufacture, release, and scalability is essential.

FUTURE DIRECTIONS:

NLCs hold significant potential in drug delivery systems. To fully realize their potential, further research should focus on scaling up production for commercial viability, exploring novel lipid combinations for enhanced performance, investigating targeted drug delivery and theranostics, and developing NLC-based formulations for gene and peptide delivery. By addressing challenges related to scale-up production, lipid selection, and targeting mechanisms, NLCs can offer more effective, safer, and personalized treatments. Their ability to improve bioavailability, provide sustained release, and enable targeted therapy makes them an exciting platform for future pharmaceutical developments. The continued exploration of NLCs in gene and peptide delivery and their application in theranostics will likely open new therapeutic possibilities across multiple medical disciplines.

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