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An Overview About Nanostructural Lipid Carriers And Its Application In Chemotherapeutics

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INTRODUCTION

Nanomedicine aims to identify and treat diseases with greater precision and efficiency while reducing side effects. It has gained traction due to its ability to deliver medications and bioactive substances to target tissues more accurately and in a controlled manner by encapsulating or attaching them to nanostructures. These drug delivery systems utilize colloidal carriers known as nanocarriers, which typically have particle sizes smaller than 1000 nm. Nanocarriers can modify the fundamental properties and bioactivity of drugs due to their high surface area-to-volume ratio. They enhance pharmacokinetics and biodistribution through passive or active targeting, resulting in reduced toxicity and improved therapeutic outcomes. Benefits include increased bioavailability, controlled drug release profiles, prolonged circulation times in the bloodstream, enhanced penetration into cells, and targeted delivery to specific sites and organs. Additionally, they provide protection for drugs against factors like humidity, pH changes, and enzymatic degradation. [1-5] Nanotechnology has transformed drug delivery and revolutionized medicine. The creation of various types of nanoparticles (NPs) ranging from 10 to 1000 nm has enhanced the delivery of many drug molecules, particularly chemotherapeutic agents, and offered innovative solutions to address numerous challenges related to their safety and efficacy. NPs have unique characteristics that make them effective drug carriers, including a high surface-to-volume ratio and a substantial functional surface area that enables easy adsorption of other compounds. [6-7]

CLASSIFICATION AND STRUCTURE OF NLC'S :

Based on the nanostructure, content, and ratios of solid and liquid lipids, NLC has been divided into three types.

a) Type I (The imperfect type)

b) Type II (The multiple O/F/W type)

c) Type III (The amorphous type)

Imperfect Crystal Type NLCs

NLC class- I, also known as amiss demitasse types, features a inadequately organized solid matrix, hence the name Imperfect Crystal NLC. This type of NLC comprises a largely disordered matrix filled with multitudinous voids and spaces that can accommodate fresh medicine motes in unshaped clusters. The blights in the demitasse chassis arise from blending solid lipids with an applicable quantum of liquid lipids (canvases). Glycerides, a type of adipose acid, can be used to modify or enhance the structure. The number of blights in the matrix plays a pivotal part in determining the parcels of a good medicine, as it can significantly increase the medicine's release due to the varying chain lengths of adipose acids and the combination of mono-, di-, and triacylglycerols. While the NLC matrix does n't readily form a largely ordered structure, the mixing of spatially different lipids enhances medicine cargo capacity, though this model tends to parade lower ruse effectiveness. [7, 8]

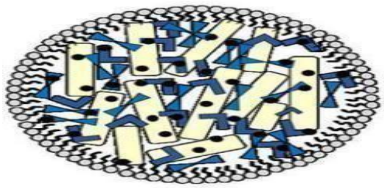


Figure No.1: Type 1 NLC

Multiple Type NLCs

The alternate type of NLC, known as" multiple" NLC, comprises a combination of oil painting, lipids, and water. This conception allows for the development of colorful NLC phrasings, as liquid lipids offer lesser solubility for lipophilic medicines compared to solid lipids at high liquid lipid attention. The lipid matrix effectively disperses small quantities of oil painting motes. still, when oil painting is added beyond its solubility limit, phase separation occurs, performing in bitsy oil painting nano- chambers girdled by the solid matrix. Type II models give several advantages, including high medicine ruse effectiveness, controlled medicine release, and reduced medicine leakage . [8-9]

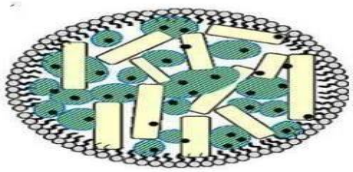


Figure No.2: Type 2 NLC

Amorphous Type NLC'S

The third type of NLC is unformed, which differs from traditional liquid NLCs by lacking distinct crystalline structures and rather featuring a disordered lipid matrix. These lipid- grounded nanocarriers retain unique parcels and advantages due to their unformed nature. To minimize medicine leakage caused by crystallization, specific lipids are strategically blended to form unformed NLCs. Certain lipids, similar as hydroxyl octacosanyl, hydroxyl stearate, isopropyl myristate, and dibutyl adipate, yield solid yet noncrystalline patches. As a result, the lipid matrix remains invariant and unformed. [7-12]

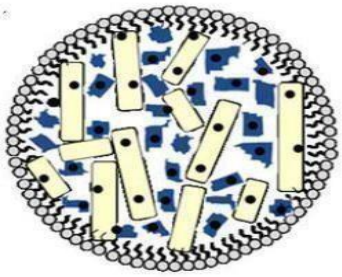


Figure No.3: Type 3 NLC

COMPARISON OF NLC WITH SLN:

SLNs have been extensively researched as drug delivery systems across various routes, including oral, parenteral, and topical administration. Their structure can be precisely adjusted based on the chemical characteristics of both active ingredients and excipients, offering several potential benefits. However, the modified release properties are influenced by the solid state of the particles, such as crystallization and other physicochemical changes. Reports indicate that inhibited or delayed crystallization can result in a reduced drug

payload. Lipid-based materials often experience physicochemical transitions, such as rearrangement of the matrix molecules. This not only leads to a more compact and organized matrix but can also change its shape, creating unfavorable conditions for many drug molecules. The drug payload is influenced not only by the physicochemical properties of the drugs being incorporated but also by the specific type of matrix material used. Drugs that cannot be integrated into the SLN matrix may instead adhere to the nanoparticle surface or potentially cause the particle matrix to separate. [3,13,14] To address the challenge of unwanted drug release during storage, a less uniform matrix is preferred. This can be achieved by utilizing a combination of different molecules. Nanostructured lipid carriers (NLCs) are created by blending varying ratios of solid and liquid lipids, typically ranging from 70:30 to 99:1. These carriers maintain a solid state at both body and room temperature. By adjusting the liquid lipid content in the formulation, better drug incorporation and immobilization can be achieved. Unlike solid lipid nanoparticles (SLNs), where drug molecules are dispersed in their molecular form, NLCs benefit from structural imperfections created by the mix of solid and liquid lipids. This results in more available spaces for drug molecules, enhancing the incorporation of drugs in both molecular and amorphous forms, and minimizing the risk of active compound expulsion during storage. Table 1 illustrates their classification by properties, emphasizing the differences between SLNs and NLCs. risk of active compound expulsion during storage. Table 1 illustrates their classification by properties, emphasizing the differences between SLNs and NLCs.

	SLN	NLC
Lipids	Use of physiological lipids; however, there is a lower stability comparatively with other materials	
Solvents	Absence of organic solvents	
Application	Application in different industries (food, cosmetic, pharmaceutical)	
Bioavailability	Improved bioavailability of drugs	
Drugs loaded	Loads both lipophilic and hydrophilic drugs; however, has difficulty in loading therapeutic proteins	
Drug delivery	Targeted drug delivery and enhanced drug permeation	
Scale-up	Cheaper and easier to scale up than polymeric nanoparticles	
Protection	Protection of drug molecules from enzymatic activity, harsh pH, and moisture	
Cytotoxicity	Cytotoxicity concerns due to the nature and concentration of matrix lipids	
Drug loading capacity	Limited drug loading capacity	Improved drug loading capacity
Controlled drug release profile	Difficulty in adjusting the drug release profile	Better controlled drug release profile
Polymorphic transitions	Prone to polymorphic transitions	No polymorphic transition takes place
Release during storage	Unwanted drug release during storage	Minimal drug release during storage
Physical stability	Possible particle aggregation or fusion during storage	Better physical stability during storage
Water content	High water content	Low water content

Table No.1: Comparison Between SLN and NLC.Advantages and Disadantages

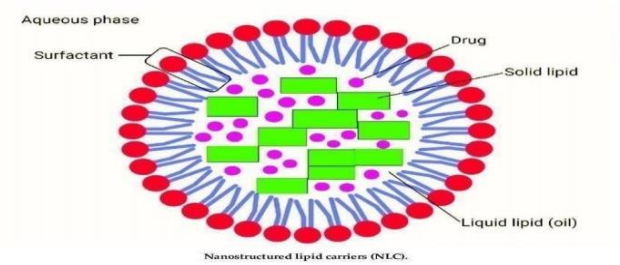
COMPOSITION AND METHOD OF PREPARATION OF NLC

Composition:

Nanostructured lipid carriers (NLCs) represent a cutting-edge approach in drug delivery systems, utilizing a blend of solid and liquid lipids to optimize drug encapsulation and release profiles. The solid lipids—such as glyceryl monostearate, stearic acid, and Compritol 888 ATO—offer structural integrity and stability, maintaining their solid state at both room and body temperatures. This rigidity forms a protective matrix around the encapsulated drug, allowing for sustained release. Complementing these solid lipids, liquid lipids (oils) like oleic acid, caprylic acid, medium-chain triglycerides (MCT), or castor oil enhance the solubility of poorly water-soluble drugs and inhibit crystallization, thus improving the carrier's flexibility and drug-loading capacity. Surfactants and emulsifiers are crucial for stabilizing NLCs and preventing particle aggregation by lowering the interfacial tension between the lipid and aqueous phases. Common surfactants such as Polysorbate 80, lecithin, sodium dodecyl sulfate (SDS), and Pluronic F68, not only stabilize the nanoparticles but also affect their interaction with biological membranes, enhancing drug absorption. The hydrophobic chemotherapeutic agent to be delivered is encapsulated within the lipid matrix or dispersed throughout both solid and liquid lipid phases. This method boosts drug bioavailability, ensures prolonged circulation, and facilitates controlled drug release,

thereby minimizing systemic side effects. The lipid mixture is usually dispersed in an aqueous phase, such as water or buffer solutions, to create a stable colloidal suspension. This aqueous environment aids in maintaining dispersion and may contain stabilizing agents to ensure optimal pH and osmotic balance. In summary, the composition of NLCs—incorporating both solid and liquid lipids along with appropriate surfactants—results in a versatile system that provides enhanced drug stability, high loading capacity, and controlled release. These characteristics make NLCs especially suitable for chemotherapeutic applications, where targeted drug delivery, reduced toxicity, and overcoming drug resistance are essential for effective treatment.

Figure No.4: Composition of NLC



Method of Preparation

The ways used for preparing solid lipid nanoparticles(SLNs) can also be applied to the expression of nanostructured lipid carriers(NLCs). These medication styles can be distributed into three main groups high-energy styles, low- energy styles, and styles involving organic detergents. crucial aspects of NLC expression development are explored, pressing the colorful advantages and disadvantages associated with each fashion. The choice of system for preparing NLCs is told by the specific parcels of the medicine and the asked flyspeck size(PS). For illustration, the high- pressure homogenization(HPH) fashion, which employs both high pressure and temperature, is one of the most constantly used styles for NLC medication. This fashion has the benefit of using elevated temperatures to reduce the density of the liquid admixture, thereby achieving a lower PS. still, a significant debit is the threat of demeaning the medicine and carrier at these advanced temperatures. Accordingly, this system is more suitable for largely lipophilic and undoable medicines rather than for hydrophilic bones. Other benefits of this technique include the elimination of organic solvents and its scalability. Conversely, the emulsion evaporation method involves heating the oil phase under reduced pressure to facilitate evaporation; while this technique helps avoid excessive heat, its primary drawback is the reliance on solvents, which may introduce toxicity from residues. Similarly, the solvent dispersion method is characterized by its speed, simplicity, and lack of need for complex equipment, but it is not suitable for large-scale production of NLCs and carries the risk of solvent residues in the final product. The microemulsion approach offers advantages such as requiring only a small amount of drug and being straightforward; however, it necessitates high concentrations of emulsifiers. [18,19]

HIGH-ENERGY APPROACHES

1.HPH technique

The HPH fashion is largely favored due to its shorter product time compared to other styles, ease of scale-up, and solvent-free process. HPH styles can be distributed into hot HPH and cold HPH protocols. The hot HPH process involves melting solid lipids, which are also blended with liquid lipids and medicines. This admixture is latterly combined with a hot surfactant result in water to produce a preemulsion. subsequently, homogenization is carried out at high temperatures and pressures(up to 500 bar) over three cycles, performing in solid lipid nanoparticles(SLNs) or nanostructured lipid carriers(NLCs). While high temperatures can lower flyspeck size by reducing lipid density, they also increase the threat of medicine or carrier system declination. In discrepancy, the cold HPH process begins with melting a lipid mix to form a dissipation of lipid microparticles, which is also mixed with a cold surfactant result to produce a presuspension. Homogenization is performed at room temperature with advanced pressures (up to 1,500 bar) for 5 – 10 cycles, yielding SLNs or NLCs as the final product. [19]

2. Melt emulsification homogenization technique

In this method, the solid lipid, liquid lipid, and drug are combined and dispersed in an aqueous surfactant solution using probe sonication. The mixture is subsequently cooled to a low temperature to produce solid NLCs. A key benefit of this technique is that it eliminates the need for heat. [18]

LOW-ENERGY APPROACHES

1. **Microemulsion technique**

In this technique, the lipid carrier is heated just above its melting point, followed by the addition of a drug, an auxiliary emulsifier, and deionized water (preheated to the same temperature) to create a transparent mixture with thermodynamic stability akin to an oil-in-water microemulsion. This mixture is then rapidly dispersed in ice-cold water (0–4°C) while gently stirring, resulting in a dispersion of nanostructured lipid carriers (NLCs). The temperature difference between the microemulsion and the cold water is crucial for controlling the size of the nanoparticles, as the rapid cooling minimizes particle aggregation, leading to smaller NLC sizes. However, there are certain disadvantages to consider. [20]

2. **Membrane contractor technique**

Lipid is transported through membrane pores under pressure that maintains the system above the lipid's melting temperature, leading to the conformation of small driblets. Meanwhile, the waterless phase circulates within the membrane, carrying along the driblets created at the pores. When the medication cools to room temperature, lipid nanoparticles(LNPs) form. The size and lipid affluence of the LNPs are affected by factors similar as the inflow haste of the waterless phase, the temperatures of both the lipid and waterless phases, the size of the membrane pores, and the pressure of the lipid phase. [19]

3. **Phase-inversion temperature technique**

The transition from an oil-in-water (O/W) emulsion to a water-in-oil (W/O) emulsion is integral to this innovative, cost-effective, and solvent-free method for synthesizing lipid nanoparticles (LNPs). In Step 1, the optimal ratios of lipid, surfactant, and water are determined, followed by raising the temperature from room temperature to 85°C. The system undergoes three temperature cycles to reach the phase inversion zone. In Step 2, the introduction of cold water (0°C) creates an irreversible shock to the system, leading to the formation of nanocapsules. [20]

4. **Coacervation technique**

This innovative solvent-free method allows for the incorporation of thermosensitive pharmaceuticals without the need for
costly equipment or hazardous solvents. When combined with a suitable amphiphilic polymeric stabilizing agent, a micellar solution of a fatty acid sodium salt gradually interacts with an acidic solution, resulting in coacervation. [20]

5. ***Double emulsification technique***

This technique, utilizing the solvent emulsification–evaporation process, is primarily employed to produce lipid nanoparticles (LNPs) that encapsulate hydrophilic drugs. In this method, the drug and stabilizer are contained within the inner aqueous phase of a water/oil/water (W/O/W) double emulsion. Because these formulations have a larger particle size compared to solid lipid nanoparticles (SLNs), they are referred to as lipospheres. [20]

APPROACHES WITH ORGANIC SOLVENTS

1.Solvent emulsification evaporation technique

The lipid is dissolved in a water-insoluble organic solvent, like cyclohexane or chloroform, and then mixed with continuous stirring into an aqueous phase that contains surfactants, creating an oil-in-water (O/W) emulsion. Solvent evaporation and lipid precipitation occur through evaporation at reduced pressure. While this method avoids heat stress, it has one significant drawback: the use of an organic solvent. [21]

2.Emulsification solvent diffusion technique

This method resembles the “solvent emulsification–evaporation” technique, but here the lipid is dissolved in a partially water-miscible organic solvent like benzyl alcohol or ethyl formate. By continuously stirring, the temporary oil-in-water emulsion is added to water, prompting the dispersed phase to solidify into lipid

nanoparticles (LNPs) as the organic solvent diffuses out. The lipid solidifies during this diffusion process. [22]

3. Evaporation solvent injection technique

A water-miscible solvent—such as acetone, ethanol, methanol, or isopropyl alcohol—or a watersoluble solvent mixture is employed to dissolve lipids. This solution is then rapidly injected into an aqueous surfactant solution while being stirred continuously. Any excess fat is removed from the resulting dispersion through filtration. This

method is advantageous because it is straightforward, efficient, versatile, does not require specialized equipment (like a high-pressure homogenizer), and utilizes approved organic solvents. [23]

4. Supercritical fluid technique

This technique involves dissolving the lipid material along with the drug in an organic solvent, such as chloroform, by adding an appropriate surfactant to create an organic solution. This organic solution is then dispersed in an aqueous phase (which may include a co-surfactant) and the mixture is homogenized under high pressure to form an O/W emulsion. The O/W emulsion is injected at a constant flow rate from one end of the extraction column (usually the top), while a supercritical fluid is introduced at a constant flow rate in the opposite direction. Continuous extraction of the solvent from the O/W emulsions facilitates the formulation of LNP dispersions. [24]

LYOPHILIZATION OF NLC

Lyophilization, or freeze-drying, is a technique used to stabilize nanostructured lipid carriers (NLCs) with the goal of extending product shelf life and protecting it from both chemical and physical degradation. This method produces a solid-state material that can easily be re-dispersed when needed. The lyophilization process relies on the principle of sublimation, where water transitions directly from a solid (ice) to a gas, bypassing the liquid phase. To safeguard the formulation during this process, cryoprotectants and lyoprotectants are incorporated as stabilizers. These agents help protect the product from the stresses of freezing and drying. Common cryoprotectants include mannitol, trehalose, fructose, sorbitol, lactose, glucose, sucrose, and aerosil, typically added at concentrations of 5–15% w/w. This method is highly reliable as it preserves the molecular structure of the product. Additionally, cryoprotectants can vitrify at a specific temperature, known as the glass transition temperature (Tg).

Nanoparticles can be bedded in a glassy cryoprotectant matrix to help aggregation and cover them from the mechanical stress caused by ice chargers. Cryoprotectants enhance the long- term stability of nanostructured lipid carriers(NLCs) during storehouse, while also acting as bulking agents, especially salutary when the product attention for snap- drying is low, and tonicity adjusters. Surfactant- stabilized NLCs developed through suitable styles may parade good stability; still, in waterless results, they can suffer from poor chemical and physical stability. Over time, issues similar as aggregation or other unlooked-for negative goods can arise. thus, enhancing the stability of NLCs and conserving their physical characteristics is decreasingly vital. multitudinous studies have employed cryoprotectants to lyophilize NLC results, securing them against agglomeration during storehouse. For illustration, Tilmicosin NLC suspense was lyophilized using mannitol as a cryoprotectant after being formulated through heat homogenization with Compritol 888 ATO, sesame oil painting, Poloxamer 407, and Tween ® 80. The performing lyophilized products demonstrated bettered longterm stability. also, NLCs containing lopinavir(LPV) and verapamil were produced using Compritol 888 ATO ® and oleic acid as solid and liquid lipids via a hot high- shear homogenization fashion. colorful cryoprotectants, including mannitol, sorbitol, sucrose, and trehalose, were screened using flyspeck size(PS) and polydispersity indicator(PDI) as criteria . Trehalose surfaced as the most effective at precluding aggregation of LPV- NLCs and enhancing stability throughout the snap- drying process. Compared to other cryoprotectants, trehalose offers several advantages, similar as reduced chemical relations and a advanced glass transition temperature, both of which can contribute to the stability of nanoparticles. Rifabutin(RFB)- NLCs, intended for tuberculosis treatment, were prepared using miglyol- 812(liquid lipid) and Precirol ® ATO 5(solid lipid) through high- shear homogenization and ultrasonication ways, with Aerosil serving as a cryoprotectant at a attention of 2 w/ w, yielding a stable expression. Olmesartan NLCs, created with Precirol ATO 5 and Capmul MCM, were lyophilized using mannitol, performing in a substantial, fluently redisperseable cutlet with a redispersibility indicator close to one, icing their long- term stability. also, mannitol was employed as a cryoprotectant in the medication of exemestane NLCs using an ultrasonication fashion, with flaxseed oil painting as the liquid lipid and Precirol ATO 5 as the solid lipid. The lyophilized expression of these NLCs demonstrated better stability compared to their suspense throughout the storehouse period. [25-27]

CHARACTERIZATION OF NLC

The characterization of nanostructured lipid carriers (NLC) involves several critical techniques to assess their physical, chemical, and functional properties, ensuring effective drug delivery. Here are some essential characterization methods:

1. **Particle Size and Zeta Potential**:

   Dynamic light scattering (DLS) is widely used to determine particle size distribution, which impacts the stability and bioavailability of the NLC. Zeta potential measurement helps assess the surface charge, which influences colloidal stability by indicating the degree of particle dispersion or aggregation in suspension.
2. **Morphological Analysis :**

   Techniques such as transmission electron microscopy (TEM) and scanning electron microscopy (SEM) provide visual insights into the shape and structure of NLC. These methods help confirm the formation of spherical or irregular particles.
3. **Entrapment Efficiency and Drug Loading**:
   Entrapment efficiency reflects the proportion of drug encapsulated within the lipid matrix, which is critical for ensuring therapeutic effectiveness. High-performance liquid chromatography (HPLC) or UV spectrophotometry can quantify both the encapsulated and unencapsulated drug content.
4. **Differential Scanning Calorimetry (DSC)**:
   DSC helps assess the thermal behavior of NLC, such as melting and crystallization points. This analysis provides insights into lipid modifications and stability upon drug incorporation.
5. **Fourier-Transform Infrared Spectroscopy (FTIR)**

   FTIR is used to investigate the chemical interactions between the drug and lipids, confirming the successful encapsulation of the therapeutic agent. This technique identifies any possible structural changes in the functional groups.

6. **In Vitro Release Studies**

   Franz diffusion cells or dialysis membrane systems simulate the drug release behavior of NLC in biological conditions. This evaluation helps predict how the drug will be released from the carrier in vivo over time.
7. **Stability Testing:**

   Long-term and accelerated stability studies evaluate how storage conditions affect the particle size, zeta potential, and drug content, ensuring the formulation remains effective during its shelf life. These characterization techniques ensure that NLC formulations meet the necessary quality parameters for pharmaceutical applications, particularly in chemotherapy drug delivery, where precise control over drug release and stability is critical. [29-30]

APPLICATION OF NLC IN CHEMOTHERAPY

Nanostructured lipid carriers (NLCs) have emerged as a promising drug delivery system in chemotherapy, addressing many limitations of conventional cancer treatments. One of the key advantages of NLCs is their ability to encapsulate poorly water-soluble chemotherapeutic agents, improving their bioavailability and enabling efficient delivery to cancerous tissues. The unique combination of solid and liquid lipids in NLCs ensures controlled and sustained release of anticancer drugs, reducing the frequency of dosing and minimizing fluctuations in drug concentration. This sustained release helps lower systemic toxicity, a major challenge in traditional chemotherapy, by limiting the exposure of healthy tissues to high drug concentrations. [16]

Another significant application of NLCs in chemotherapy is their ability to achieve targeted drug delivery. NLCs can be functionalized with ligands, such as antibodies or peptides, that specifically recognize and bind to receptors overexpressed on cancer cells, enhancing the precision of drug delivery. This targeted approach increases the therapeutic efficacy of the drugs while minimizing side effects, as fewer drugs interact with healthy cells. Additionally, NLCs can penetrate biological barriers, such as the blood-brain barrier, making them suitable for treating cancers in hard-to-reach areas, such as glioblastomas. [31]

NLCs also offer the potential to address multidrug resistance (MDR), a common problem in chemotherapy where cancer cells become resistant to therapeutic agents. By encapsulating multiple drugs within the same carrier, NLCs can deliver combination therapies in a synchronized manner, helping to overcome resistance mechanisms. Furthermore, the lipid matrix can inhibit drug efflux by cancer cells, ensuring higher intracellular drug concentrations. In conclusion, the application of NLCs in chemotherapy offers several advantages, including

improved drug solubility, controlled release, targeted delivery, and the potential to overcome multidrug resistance, making them a valuable tool in the advancement of cancer treatment strategies. [32]

FUTURE PROSPECTS

The future of nanostructured lipid carriers (NLCs) in chemotherapy is promising, with ongoing research focused on optimizing their design for enhanced therapeutic outcomes. Advancements in surface engineering and ligand functionalization are expected to improve targeted drug delivery by binding NLCs to tumor-specific markers, thereby further minimizing side effects. Additionally, there is significant potential for NLCs to be combined with other therapies, such as immunotherapy or photodynamic therapy, offering synergistic effects against cancer. Future studies may also explore personalized medicine approaches by tailoring NLC formulations for individual patient needs based on tumor genetics and drug resistance profiles. Research into biodegradable and biocompatible materials will further enhance the safety and applicability of NLCs. Largescale clinical trials and regulatory approval are needed to validate their clinical efficacy and establish standardized protocols for large-scale production and use in cancer treatment.

CONCLUSION

Nanostructured lipid carriers represent a significant advancement in the field of drug delivery, particularly in chemotherapy. Their ability to improve drug solubility, provide controlled release, and offer targeted delivery makes them a valuable tool in overcoming the limitations of conventional chemotherapy, such as systemic toxicity and multidrug resistance. The modular nature of NLCs allows for flexibility in drug loading and customization, making them suitable for various anticancer agents. Although challenges remain, including large-scale manufacturing and regulatory hurdles, the ongoing research into NLCs suggests that they could play a vital role in the future of cancer treatment by enhancing therapeutic efficacy while minimizing adverse effects.

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