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NANOSTRUCTURED LIPID CARRIERS (NLCs): A COMPREHENSIVE REVIEW OF DRUG DELIVERY ADVANCEMENTS

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ABSTRACT
Background: Nano-structured lipid carriers (NLCs) have emerged as a significant advancement in lipid-based drug delivery systems. Compared to Solid Lipid Nanoparticles (SLNs), NLCs offer improved drug loading capacity, stability, and controlled release profiles. **Objective:** This review article explores the structural and functional benefits of NLCs, their enhanced bioavailability, and their potential in targeted therapeutic agent delivery. **Methodology:** We investigated the unique combination of solid and liquid lipids in NLCs, which creates an internal structure for improved drug encapsulation and sustained release. Various methods were analyzed for their contribution to NLC efficacy, including high-pressure homogenization and solvent emulsification. **Results and Discussion:** NLCs demonstrated encapsulation efficiency ranging from 85–95%, with particle sizes between 100–300 nm. Drug release was sustained over 24 hours, affirming their effectiveness in controlled drug delivery. Applications of NLCs were highlighted across diverse delivery modes, including topical, pulmonary, oral, parenteral, and ocular. Challenges such as scaling production, overcoming biological barriers, and ensuring regulatory compliance were also addressed. **Conclusion:** NLCs present a promising future in pharmaceutical sciences, with the potential to improve therapeutic outcomes in complex diseases like cancer and neurodegenerative disorders. Continued research into NLC formulations is critical for advancing patient outcomes and addressing global health challenges.

INTRODUCTION

Lipid-based drug delivery systems have been created recently to address challenges like low drug absorption and targeted delivery, improving how drugs reach specific sites for practical pharmacological effects [1]. Several United Nations Sustainable Development Goals (SDGs) are supported by NLCs: SDG 3, Good Health and Well-Being, links improved treatment outcomes through enhanced drug delivery; SDG 9, Industry, Innovation, and Infrastructure, embraces pharmaceutical innovation and infrastructure; and SDG 12, Responsible Consumption and Production, encapsulates sustainable medication use to prevent waste [2]. Lipid nanoparticles enhance

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solubility and stability of hydrophobic drugs, protect against enzymatic degradation, and allow for targeted delivery, as seen in Alzheimer's treatment using curcumin-loaded NLCs [3], and Lipid nanoparticles enhance drug solubility and stability, protect against enzymatic degradation, and improve targeted delivery, as seen in vitamin D3-loaded NLCs demonstrating stable release and increased bioavailability over 20 days [4]. Lipid nanoparticles (LNPs) provide various benefits, including shielding pharmaceuticals from degradation within the body, increasing their solubility and efficacy, allowing accurate drug delivery to the afflicted region, managing drug release, and changing drug distribution throughout the body [5]. For this reason, drug delivery has changed thanks to nanotechnology, which has altered medicines. Creating various nanoparticles (NPs) of diverse sizes (10-100nm) allowed better delivery of myriad molecules. It offered non-conventional and alternative advanced vehicles to tackle some significant limitations associated with its safety and efficiency. SLNs and NLCs have been developed, colloidal particles with a 10-1000nm size range [6]. SLN emerged as the initial generation of solid lipid carrier systems at the nanoscale, with NLCs regarded as the subsequent evolution, marking the second generation beyond SLNs [7].

SLNs and NLCs enable the microencapsulation of both hydrophilic (water-loving) and hydrophobic drugs (water-fearing) with greater efficiency compared to liposomes, achieving higher entrapment efficiencies (EEs) [8]. When used as drug carriers for drugs, solid lipid nanoparticles (SLNs) face challenges such as low efficiency in loading drugs and an increased risk of drug expulsion from the formulation during storage due to polymorphic transitions [9]. Moreover, they will reorganize the structured pattern of crystals to achieve excellent stability and initiate gel formation within the dispersed phase. This results in drug leakage from the carriers and the aggregation of particles over time during storage [10]. Therefore, to overcome these constraints, researchers are selecting (NLCs) that combine solids and lipids within the core, making a much less organized structure [11]. While SLNs offer advantages like enhanced stability, they face issues such as polymorphic transitions and limited drug-loading capacity. NLCs address these limitations by incorporating liquid lipids into the matrix, improving entrapment efficiency and stability [12]. The kind of lipid used is the fundamental distinction between SLNs and NLCs. SLNs comprise solid lipids, whereas NLCs are modified by adding liquid lipids [13,14]. This unique composition enhances the rate of drug delivery and increases drug loading compared to solid lipid nanoparticles (SLNs), as seen in Figure 1. Drug entrapment efficiency and retention of drugs in the body depend heavily on the equilibrium between liquid oil (caprylic triglyceride), surfactant (polysorbate 80), and solid lipid (acetyl palmitate) [11]. Significant positive research has been done on the impact and effectiveness of nanostructured lipid carriers. NLCs have been developed as improvements over previous lipid-based systems with their limitations. The delivery of drugs with negligible water solubility can be very efficiently done using nanoparticles [15].

NLCs are spherical particles that include oil droplets within a solid lipid matrix. The presence of imperfections within the lipid matrix of NLCs creates amorphous regions, allowing for higher drug encapsulation capacity and increased drug payload [16].

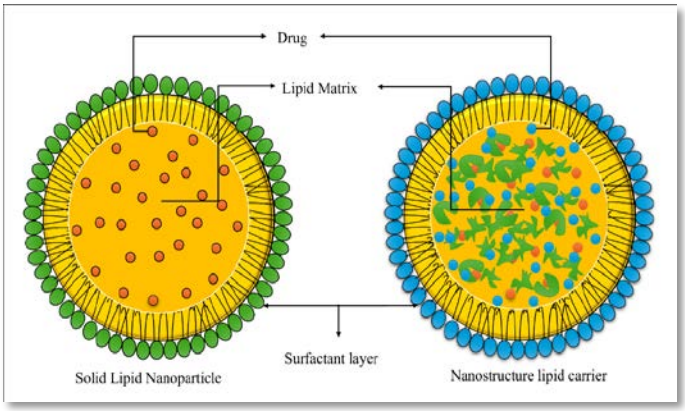

Figure 1: Showing the structure of Solid lipid nanoparticles and nanostructure lipid carrier

The contribution of this study is as follows. This review explores how NLCs, with enhanced bioavailability and stability of various active pharmaceutical ingredients, offer new solutions for modern drug delivery systems. It underlines possible applications of NLCs in several therapeutic areas, thereby highlighting their versatility and effectiveness in improving the drug delivery of various medical conditions. Additionally, this review compares NLCs with other lipid-based carriers, such as SLNs, explaining their unique advantages. Furthermore, it examines the prospects of NLCs, including views on the challenges and possibilities for further research and development. This review emphasizes the evolution of NLCs, detailing the transition from SLNs to NLCs, and uniquely discusses their applicability in emerging fields such as RNA/DNA delivery and immunotherapy, which have not been comprehensively covered in prior reviews.

Existing literature lacks a detailed exploration of NLCs' scalability and their application in advanced therapies like combination treatments. This review addresses these gaps by analyzing recent advancements and proposing strategies to improve their clinical translation.

The structure of this study is organized based on the structure and classification of NLCs, methods for the preparation of NLCs, and their applications in the drug delivery system. The next section of the research elaborates on using NLC-based drug delivery systems for treating various disorders, such as those related to the lungs, like COPD, TB, and ALI, but also Alzheimer's disease, Parkinson's disease, epilepsy, and ischemic stroke. Then, the prospects of NLC utilization are analyzed, which concludes the discussion [17].

Structure and Classification of NLCs

NLCs are generated by combining solid and liquid lipids (SL and LL), which are spatially incompatible. In this formulation, neither the solid lipid crystals nor the oil molecules from the liquid lipid phase dissolve into the liquid lipids. Instead, they integrate into the crystalline arrangement of the solid lipids. However, when cooled below their different melting temperatures, this lipid blend must remain homogenous and not separate into various phases. As a result, the formulation's solid crystalline matrix contains the liquid lipids as nano-sized pockets [18,19]. Figure 2 shows that NLCs can be categorized into three types based on their lipid content and manufacturing process.

1. Imperfect type
2. Multiple type
3. Amorphous type

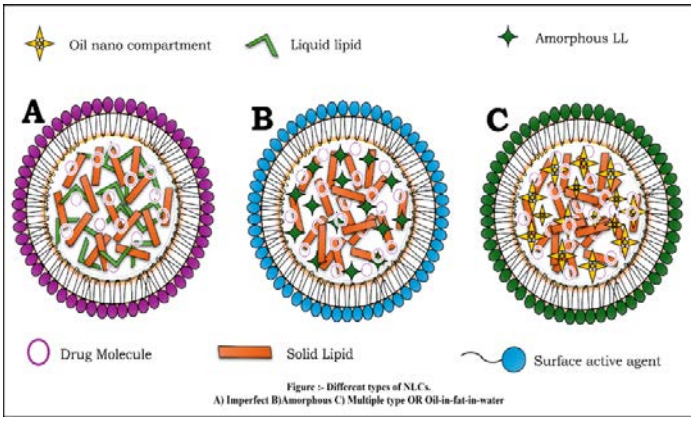

Figure 2: Structure of Nanostructured Lipid Carriers (NLCs), A) Imperfect B) Amorphous C) Multiple type OR Oil-in-fat-in-water.

Imperfect type: Imperfect NLCs are created by mixing lipids generated from various fatty acids, resulting in many defects in the crystal lattice that can store lipid-soluble medicinal molecules. This type of NLC, often called type I or imperfect crystal type, features a poorly structured solid matrix. The structure can be enhanced and modified by using various fatty acids like glycerides, increasing the total number of imperfections in the lattice [20]. These imperfections play a crucial role in strengthening drug-loading capacity. Additionally, adding small quantities of liquid lipids further increases drug-loading efficiency by preventing drug molecules from forming overly ordered crystals or amorphous clusters within the matrix [21].

Amorphous type: The amorphous variety of NLCs, also known as type III NLCs, is prepared by mixing liquid lipids (LL) that solidify into an amorphous state with solid lipids (SL). This unique combination reduces the risk of drug expulsion caused by lipid matrix crystallization, resulting in a non-crystalline, structureless matrix[22]. Unique lipids such as isopropyl palmitate, hydroxy octacosanol hydroxyl stearate, or medium-chain triglycerides (MCT) are added to enhance this formulation further. These unique lipids play a crucial role in boosting the activity and ensuring the development of solid but non-crystalline NLCs [23].

Multiple types: The kind of NLCs that are oil-in-water, often called type II or numerous types, comprises a formulation with higher oil solubility than solid lipids. In this specific kind of NLC, considerable proportions of oil are mixed with solid lipids, thus making the dispersion of oil molecules within a lipid matrix possible even at low concentration levels. These NLCs have several liquid oil nano-compartments trapped within a solid lipid matrix [24].

Such features provide a higher solubility environment than pure solid lipids for loading lipophilic drugs into these compartments for delivery. Such properties make type II NLCs more efficient in drug loading than any other class prevalent today. Moreover, since such compartments exist inside a matrix made up entirely of solids, they serve as a barrier preventing drug losses while ensuring controlled slow-release [25].

After understanding the foundational principles of lipid-based drug delivery and the advantages of NLCs, we now focus on the

methodologies employed in their formulation. These methods are critical to achieving the desired characteristics of NLCs, including improved drug encapsulation and stability (Table 1) [26]. Solid lipids like glyceryl monostearate enhance structural integrity, while liquid lipids like oleic acid improve flexibility and drug solubility. Surfactants such as Tween® 80 stabilize the emulsion, reducing particle size and improving bioavailability [27].

Table 1: Potential summary table comparing Nanostructured Lipid Carriers (NLCs) with other lipid-based systems regarding efficiency, cost, and scalability

Aspect	Nanostructured Lipid Carriers (NLCs)	Solid Lipid Nanoparticles (SLNs)	Liposomes	Lipid Nanoparticles (LNPs)	Ref.
Efficiency	High; improves drug solubility and bioavailability; enables targeted delivery	Moderate; good drug solubility and stability but lower bioavailability than NLCs	High; effective encapsulation and release properties	High; enhances solubility and stability of drugs	[28]
Cost	Moderate to High; depends on formulation and production scale	Moderate; simpler production process than NLCs	High; complex and costly production	Moderate to High; cost varies with production methods	[29]
Scalability	High; potential for industrial-scale production with microfluidics	High; well-established production methods	Moderate; challenges with scaling up without altering properties	High; advanced methods support large-scale production	[29,30]

METHOD OF PREPARATION OF NLCs

High-Pressure Homogenization: When creating drug-loaded Nano-Structured Lipid Carriers (NLCs), cold high-pressure mixing and hot, high-pressure mixing—known as cold HPH and hot HPH—are the most frequently employed. When medications are prepared using a combination of melted liquid lipids and solid lipids it is referred to as hot HPH. The mixture of the lipids and hydrophobic drug in hot conditions is then homogenized using a high-pressure solvent evaporator with 3–5 cycles to mix them well with a heated water-based solution containing both hydrophilic (such as Tween) and amphiphilic surfactant (such as lecithin). This process compels the hydrophobic phase into a small region of the homogenizer, resulting in the formation of tiny dispersed particles in submicron size range [31,32]. HPH provides various benefits, including greater processing temperatures that result in smaller particle size due to the decreased viscosity of the lipid phase [33]. However, the use of hot HPH to prepare drug-loaded NLCs has limitations. These include the drug's sensitivity to heat, low entrapment efficiency, and decreased drug-loading capacity, which can happen if the drug molecules move into the hydrophilic phase during lipid crystallization [34]. Hot HPH has several disadvantages. To solve this issue, we can use (HPH) at cold temperatures and pressures, typically below room temperature. In this method, the lipid melts, and the drug is frozen using liquid N2 or dry ice [35]. Having demonstrated new possibilities for cold high-pressure homogenization in advancing nanostructured lipid carriers allows improved chances to encapsulate thermos-labile drugs with effective enhancement of drug-loading capacity. This consists of heating the mixture of drugs using lipids until it melts and cools down quickly by immersing it in dry ice or liquid nitrogen Shown in Figure 3 (a). This rapid cooling increases the speed at which solid lipids (SL) form crystals. The particles are then reduced to 50-100µm and broken into smaller nanoparticles (NPs) by emulsifying them in a cold aqueous phase using a high-pressure homogenizer [36]. While this method reduces thermal exposure, the resulting nanoparticles vary in size. This method allows NLCs to transport hydrophilic and lipophilic medicines because it reduces drug diffusion into the aqueous media [37]. While high-pressure homogenization remains a widely used method due to its efficiency in producing smaller particle sizes, solvent emulsification offers unique advantages for heat-sensitive drugs, expanding the flexibility of NLC formulations [38].

Solvent Emulsification/Evaporation: In this procedure, the medication and lipid combination are dissolved in a water-immiscible organic solvent, meaning it doesn't mix with water. Next, ultrasonication or high-shear homogenization is used to emulsify the resultant solution in a water-based phase [32]. This approach is ideal for making NLCs with heat-sensitive drugs since it uses low pressure rather than high temperatures to remove the organic solvent and precipitate the drug-loaded NLCs, as shown in Figure 3 (b). This method ends with a significant disadvantage: including organic solvent residues in the finished product may harm the administration [39]. In addition, this approach could also entail another filtration step that may not be feasible on an industrial scale, which could result in a decreased percentage yield [40]

Microemulsion: Microemulsion is one of the most popular, widely, and frequently employed methods for creating nanostructured lipid carriers (NLCs). It is favored for its cost-effectiveness and versatility in handling polar and non-polar drugs (Table 1). An emulsion created with melted fat oil or any other modifications should be prepared by incorporating it into surfactants and co-surfactants dissolved in a water solution containing these compounds, such as sodium dodecyl sulfate. The proportions of the used will determine whether it is an o/w or a w/o emulsion to take form. This makes it thoroughly mix until small sizes like microns are achieved [41–43]. Nanostructured lipid carriers (NLCs) are made by mixing this tiny emulsion with a cold watery mixture, i.e., the Hydrophilic phase, when it is mixed at a ratio of 1:25 to 1:50 with gentle stirring; this process results in the reduction of particle size [44].

High-speed homogenization or ultrasonication: This method consists of melting lipids and then supplementing them with an active drug. After heating the surfactant solution to the same temperature, the melt was added, and a high-speed stirrer was used to emulsify the mixture [44]. NLCs are produced by ultrasonication or high-speed homogenization and often have wide size variations and moderate stability. Probe-based sonicators can improve the homogeneity of particle size distribution for NLCs with a narrow range, but metal dispersion from the probe is always an issue. This approach eventually saves both time and energy. However, NLCs created by ultrasonication have downsides such as possible contamination from metals, particles clumping together over time, and reduced stability of the NLCs, as shown in Figure 3 (f) [45].

However, because this method is simple and straightforward and uses equipment like ultrasonicators and high-shear homogenization that are widely available in production facilities and research, this technique is preferred over more complex high-pressure homogenization (HPH) for creating drug-loaded NLCs [46]. Methods like high-pressure homogenization require careful optimization to maintain uniform particle size during large-scale production, while solvent emulsification presents challenges in removing residual organic solvents, impacting scalability [47].

Phase Inversion Method: The emulsion's phase inversion caused by temperature is the basis for this technique. This procedure depends on using unique surfactants whose behavior varies with temperature. These surfactants are non-ionic, meaning they don't carry an electric charge, and they are designed to work differently depending on whether the temperature is high or low. At lower temperatures, the surfactant is expected to have a high HLB due to the significant hydration of its hydrophilic groups, which makes it water-soluble in theory. *(i.e., the surfactants love water more because their molecule is hydrated).* But when the temperature rises, their HLB value decreases because ethoxy groups become dehydrated *(i.e., the molecule loses some water-loving ability because it dehydrates).* PIT or Phase Inversion Temperature is the temperature at which a surfactant molecule is on the same level of attraction for both lipophilic and hydrophilic phases [48].

A water-in-oil (w/o) emulsion is produced when the temperature rises over the phase inversion temperature. Conversely, an oil-in-water (o/w) emulsion occurs when the temperature falls below this threshold. The structure of the emulsion is determined by this temperature-induced phase inversion, which dictates whether water droplets are disseminated in oil or vice versa [49]. During this procedure, lipid oils, water, and surfactants are combined and heated above the phase inversion temperature. This lets them form a water-in-oil emulsion through a magnetic stirrer [50]. After that, heat and cool the mixture thrice at 85°C, 60°C, and -85°C.

During this heating period, the surfactant undergoes dehydration, i.e., it loses water molecules, thereby changing its hydrophilic-lipophilic balance. When it is followed rapidly by a cooling (in an ice bath), it induces a phase inversion from w/o to o/w emulsion, and the surfactant regains its hydrophobicity,

which aids in the formation of nanostructured lipid carriers (NCLs) [51]. This innovative method offers the significant benefit of incorporating thermolabile drugs into formulations without organic solvents [52,53].

Supercritical fluid-based method: Supercritical fluids have diverse applications in fields like extraction, green chemistry, and chromatography. Researchers have recently begun investigating their potential for producing micro- and nanoparticles. However, its use in particle generation has also considerably developed during the last few decades. A supercritical fluid indicates a substance that can exist as a gas and a liquid above its critical pressure & temperature. Its characteristics distinguish it from liquids or gases in everyday situations [54]. Supercritical carbon dioxide is widely used as a supercritical fluid due to its availability, inert nature, non-flammability, and ease of attaining critical conditions (about 73.8 bar for pressure and about 31°C for temperature) [55].

Using an organic solvent, a lipid emulsion is first made. After that, the emulsion is quickly extracted using supercritical fluids, effectively removing the solvent and stabilizing the lipid particles. These procedures guarantee the lipid-based system's successful development while preserving the intended emulsion characteristics—the quick extraction method results in the precipitation of lipids and habitually sized NLCs. Concerning traditional methods like evaporation or dilution, this method has the potential for greater efficacy in solvent extraction, as shown in Figure 3 (d) [56].

Solvent Injection Method: Another name for this is the "solvent displacement technique [57]. The quick and easy formation of lipids from their dissolution in a water-miscible solvent is done using the solvent injection. This solution is quickly injected through a needle into an aqueous system containing surfactants. This method includes mixing lipids and medicines in a water-soluble solvent, such as methanol, ethanol, acetone, isopropanol, or a mixture of these solvents, as shown in Figure 3(e). Aqueous phase (water phase) is usually achieved by dissolving an emulsifier or mixture in a water/buffer solution [58]. Therefore, the needle continuously stirs the aqueous phase and simultaneously introduces the organic phase rapidly under mechanical agitation. This technique provides the benefits of straightforward preparation and avoids the need for high heat, excessive shear stress, or complex equipment. However, its drawbacks include the possibility of organic solvent residue, which can achieve high particle concentrations [59].

Double emulsion method: - This method is widely used for drugs that are (water-loving) Hydrophilic drug and also for drugs that are sensitive to temperature. The double emulsion method is employed to manufacture drug/biomolecule (such as proteins and peptides) loaded NLCs [60–62]. This technique produces a water-in-oil (w/o) emulsion by combining a hydrophilic medication dissolved in an aqueous medium with a lipid melt containing lipophilic surfactants Shown in Figure 3 (c).

The next step involves adding this primary emulsion to an aqueous solution containing a hydrophilic solvent, creating a double emulsion that is water-in-oil-in-water (w/o/w). The Nanostructured Lipid Carriers (NLCs) are then separated from the dispersion by ultrafiltration and solvent evaporation. It has been frequently utilized to integrate insulin in NLC matrices for oral medication delivery applications (Table 2) [63,64]. The double emulsion method has an advantage over the single because it does not require a molten lipid phase [65]. Once these methods optimize the preparation of NLCs, their practical applications across various drug delivery systems become evident.

Despite substantial advances and promise, Nanostructured Lipid Carriers (NLCs) face various hurdles in their broad implementation. Scaling manufacturing is a significant difficulty. While laboratory-scale synthesis processes, such as high-pressure homogenization and solvent emulsification, have proved useful, the shift to industrial-scale production frequently presents challenges in preserving uniform quality and efficiency [86]. Furthermore, the endurance of NLCs over a longer period must be addressed because stability might be disturbed during storage and transit, resulting in drug ejection or degradation.

Another major impediment is the biological issues connected with medication delivery. To achieve therapeutic effectiveness, NLCs must successfully transit biological barriers that include cellular membranes & the blood-brain barrier. Further study into changing the surface properties of NLCs, such as using targeted ligands or optimizing lipid content, may improve their capacity to traverse these barriers [87]. Addressing these obstacles via ongoing research & innovation will be critical to effectively implementing NLCs in clinical practice.

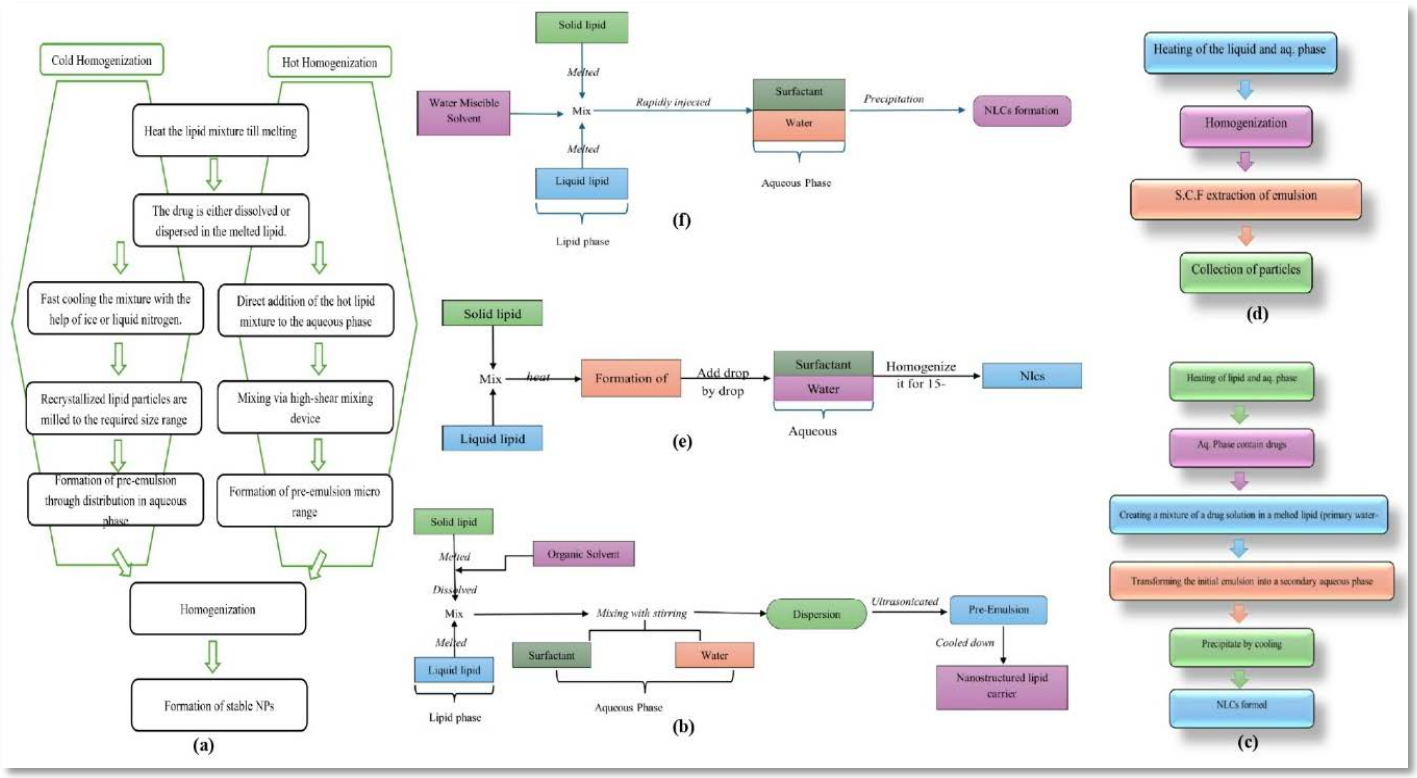

Figure 3: Different methods for the preparation of NLCs. a). High Pressure Homogenization method, b) Solvent emulsification/evaporation method, c) Double emulsion method, d) Supercritical fluid-based method, e) Solvent injection method, f) High speed Homogenization method.

Nanostructured Lipid Carriers (NLCs) are increasingly recognized for their advanced therapeutic applications, particularly in RNA/DNA delivery and immunotherapy. Recent studies demonstrate their ability to encapsulate and protect nucleic acids from enzymatic degradation, achieving encapsulation efficiencies exceeding 95% with particle sizes ranging from 100-300nm, which ensures enhanced stability and cellular uptake [88]. For instance, lipid nanoparticles (LNPs), a subclass of NLCs, played a critical role in mRNA vaccine delivery during the COVID-19 pandemic, showcasing their efficacy in genetic and infectious disease therapies. Similarly, mannose-functionalized NLCs have proven effective in delivering DNA vaccines, significantly enhancing tumor-specific immune responses [89,90].

In immunotherapy, NLCs facilitate the targeted delivery of cytokines and tumor antigens, reducing systemic toxicity and improving immune activation, as evidenced by their success in cancer immunotherapy trials. Despite these advancements, challenges such as long-term stability, scalability, and immune response modulation remain. Future research should focus on optimizing lipid compositions, improving manufacturing technologies, and conducting rigorous clinical evaluations to harness NLCs' potential in next-generation therapeutics fully [90,91].

Applications of Nanostructured Lipid Carriers (NLCs) in Respiratory and Neurological Disorders

Asthma: Asthma is a chronic inflammatory lung condition characterized by airway narrowing and inflammation, primarily driven by immune elements such as eosinophils, CD4 T lymphocytes, and mast cells (Table 3).

Current treatments, including inhaled corticosteroids and bronchodilators, often lead to side effects like lung remodeling and immunosuppression. NLCs offer a promising alternative by improving drug delivery and reducing side effects [92]. For example, montelukast-loaded NLCs [108].

Demonstrated high encapsulation efficiency (>95%) and improved safety and efficacy, as detailed in Table 3. Similarly, beclomethasone-loaded NLCs showed controlled drug release and effective targeting of deep lung tissue [93]. Although NLCs

are generally biocompatible, several concerns remain regarding their long-term safety. Potential side effects include immune system activation, cytotoxicity from residual surfactants, and accumulation in non-target tissues. Additionally, the stability of lipid matrices during storage can affect drug release profiles, leading to unintended systemic effects. Rigorous in vivo studies and long-term safety assessments are essential to address these issues and ensure clinical viability [94].

Table 2: Application of NLCs in various drug delivery

Route of Administration	Drug Name	Disease/Application	Reference
Topical	Donepezil	Alzheimer	[66]
	Ketoprofen	Arthritis and skin inflammation	[67][68]
	Meloxicam	Osteoarthritis and rheumatoid arthritis	[69]
	Fluticasone	Atopic dermatitis and psoriasis	[43]
	Nanolipid Q 10 CL	Antioxidants that prevent aging in the cells (Anti-aging).	[70,71]
Pulmonary	Montelukast sodium	Prophylaxis and treatment of chronic Asthma	[72]
	Itraconazole	Fungal lung infections	[73]
	Sildenafil	Pulmonary arterial hypertension	[74]
oral	Repaglinide	Diabetes	[75]
	Simvastatin	Antihyperlipidemic	[14]
	Apomorphine	Parkinson's disease treatment via brain targeting	[76]
	Buprenorphine	Analgesic therapy for long-term pain and opioid addiction	[77]
Parenteral injection	Baicalein	Brain targeting for prevention or therapy of ischemic brain damage and neurodegenerative diseases	[78,79]
	Bromocriptine	Neuroleptic malignant syndrome, pituitary tumors, and Parkinson's disease can all be treated by brain targeting.	[80]
	Apomorphine	Parkinson's disease treatment via brain targeting	[76]
	Buprenorphine	Analgesic therapy for long-term pain and opioid addiction	[77]
Ocular	Mangiferin	Cataract	[81]
	Moxifloxacin	Treatment of endophthalmitis	[82]
	Triamcinolone Acetonide	Inflammatory and angiogenic ocular diseases	[83,84]
	Flurbiprofen	Anti-inflammatory	[85]

COPD (Chronic Obstructive Pulmonary Disease):

COPD, a leading cause of death globally, is characterized by chronic bronchitis and emphysema, often exacerbated by alpha-1 antitrypsin deficiency. Key immune players include neutrophils, CD8 T lymphocytes, and macrophages, with excessive mucus production and inflammation being major challenges. NLCs offer a promising approach to targeted drug delivery. For instance, rosuvastatin-loaded NLCs demonstrated stable particle size (165 nm) and high fine particle fractions (>90%), confirming their efficacy in COPD treatment (Table 3) [95].

T.B. (Pulmonary Tuberculosis):

Tuberculosis, caused by Mycobacterium tuberculosis, remains a global health challenge, with 10.6 million new cases reported in 2023. *(World Health Organization. (2023). Global tuberculosis report 2023.* https://www.who.int/publications/i/item/9789240068240).

NLC-based formulations, such as rifampicin and rifabutin-loaded NLCs, have shown potential to improve therapeutic outcomes by targeting alveolar macrophages and enhancing drug stability (Table 3) [96,97].

Acute lung injury (ALI): This condition, or ARDS or ALI, is characterized by intense inflammation caused by damage to the lung's endothelial and epithelial barriers (Table 3). It leads to reduced oxygen levels in the bloodstream [98]. Simvastatin-loaded NLCs, conjugated with anti-ICAM1 antibodies, demonstrated high encapsulation efficiency (91.04%) and effective lung targeting in murine models [99]. Similarly, nanostructured lipid carriers showed significant anti-inflammatory effects in ALI treatment. [100].

Neurological Disorders: Nanotechnology has made available a widening range of medical tools and therapies for physicians to use in their work, as well as nanomedicine. The application of nanotechnology to medicine has offered specific solutions for medical diagnosis, prevention, and treatment of diseases[101]. Conventional drug delivery systems for neurological disorders often lack target specificity, leading to toxicity and reduced efficacy. NLCs, with their ability to cross the blood-brain barrier, offer a promising solution for targeted drug delivery to the central nervous system (Table 3) [102].

Alzheimer's Disease (AD): AD, responsible for 70% of dementia cases, is characterized by cognitive decline and oxidative stress. NLCs have shown promise in enhancing drug delivery to the brain (Tabel 3). For example, curcumin/donepezil-loaded NLCs improved cognitive function and reduced oxidative damage in rat models. Similarly, astaxanthin-loaded NLCs demonstrated high encapsulation efficiency (94.1%) and effective nose-to-brain delivery, offering potential alternative to oral administration (Table 3) [103] [104] [105].

Parkinsonism: Parkinson's disease (PD) is another condition that leads to various central nervous system issues in the elderly. It is primarily marked by a reduction in dopamine levels in the basal ganglia and a progressive loss of dopaminergic neurons in the substantia nigra [106]. Most of the current treatment options for PD are entirely symptomatic, while primary therapy revolves around restoring dopamine or anticholinergic effects (Table 3) [107].

Epilepsy: Epilepsy, characterized by recurrent seizures, poses significant challenges in drug delivery due to the blood-brain barrier [108]. NLCs, such as **phenytoin-loaded and valproic acid-loaded** formulations, have demonstrated sustained drug release and enhanced brain targeting. For instance, **lamotrigine-loaded** NLCs showed high drug-loading efficiency (97%) and prolonged therapeutic effects in rat models [109] [110].

Ischemic stroke: Ischemic stroke, caused by reduced blood flow to the brain, leads to neuronal damage and oxidative stress. Ferulic acid-loaded NLCs minimized cytotoxicity and oxidative stress in rat models, while rivastigmine-loaded NLCs improved brain targeting and pharmacodynamics, facilitating recovery from amnesia. (Table 3) [111] [112].

Table 3: NLC formulation is used in the treatment of different disorders.

Disorder	NLCs Formulation	Method's	Route	Key finding	Ref
Asthma	MN-NLCs (Montelukast-loaded NLCs)	Melt emulsification-Ultrasonication method	Parenteral Route	The NLCs had a high entrapment efficiency (>95%) and an average particle size of 184.6 nm. In-vitro cytotoxicity and pharmacokinetic evaluations showed that they improved their safety & effectiveness.	[72]
	BDP-NLCs (Beclomethasone loaded NLCs)	High-pressure homogenization to form Aerosols	Pulmonary Route of Administration.	The lipid nanoparticles had a 99% entrapment efficiency, with a diffusion-controlled release and targeted delivery to the deep lungs.	[113]
COPD	RSVS (Rosuvastatin) loaded NLCs as (RNLC-DPI) Dry powder for inhalation	Emulsification-Ultrasonication method	I.N (Intranasal Route)	Stable Particle size, high fine particle fraction (FPF) of over 90%, and demonstrated effective in-vivo Treatment for COPD.	[95]

Disorder	NLCs Formulation	Method's	Route	Key finding	Ref
T.B (Pulmonary TB)	Man-INH-NLC (Mannitol-Isoniazid-Nanostructured Lipid Carriers)	Hot homogenization-ultrasonication technique		Safely improve the dosage regimen and therapeutic efficacy.	[114]
Acute lung injury (ALI)	S.V (simvastatin) loaded NLCs	Solvent diffusion method	Intra-tracheal inj	Found that the larger NLCs (337.8nm) had a higher encapsulation efficiency (%EE) of 91.04% compared to smaller NLCs, which had an EE of 66.70%	[99]
	NLCs (Nanosized phospholipids / Triglyceride particles)	Solvent emulsification method.	I.V (Intravenous route)	The lipid nanoparticles showed potent in vitro uptake in mouse lung cells and significant anti-inflammatory effects in a murine ALI model.	[100]
Alzheimer's Disease	(Curcumin/Donepezil) loaded NLCs	Microemulsion technique	I.N	Particle size = <50nm, EE% = 94.16+-0.31). Increased drug concentrations in the brain enhanced memory and learning, elevated acetylcholine (Ach) levels, and reduced oxidative damage.	[103]
	VIN-NLC (Vinpocetine-Nanostructured Lipid Carriers)	HPH method	Oral route	Bioavailability was increased 2-5-fold with sustained and no burst releases, significantly improving cognition and memory.	[115]
	RSV (resveratrol)-NLCs	Interfacial polymerization	Intra-peritoneal inj	Targeting the brain directly, providing a steady release of the medication, achieving 4- to 6-fold more excellent absorption, and resulting in a notable decrease in spontaneous alternation and object recognition memory.	[104]
	AST (Astaxanthin)-loaded NLCs	Hot HPH method	I.N	The results we obtained indicate that IN administration of Astaxanthin in NLC could serve as an appropriate treatment for Alzheimer's disease & address its low oral bioavailability.	[105]
	BER-CST-NLCs (Braberine-Nanostructured lipid carrier overloaded with chitosan)	Hot homogenization and ultrasonication method		The development of NLCs of BER is boosting the effect of BER in CNS diseases such as Alzheimer's disease.	[116]
Parkinson	[NLC-DOPA] (Dopamine-loaded NLC)	Homogenization method	I.N.	It increased the drug's bioavailability in brain with reduced toxicity, showing effective treatment of P.K.	[117]

Disorder	NLCs Formulation	Method's	Route	Key finding	Ref
	NLCs (chitosan-coated for the delivery of Tanshinone IIA)	Simple melt-emulsification ultrasonication method		Show good colloidal particle size <200nm, High dose entrapment efficiency (>97%), sustained release profile of 24hr	[118]
	RP-HLC loaded NLCs (Ropirinole-Hydrochloride loaded NLCs)	Homogenization method	I.V	Enhanced absolute bioavailability	[119]
	TFM-NLCs (Teriflunomide-loaded NLCs)	Melt-emulsification Ultrasonication method.	I.N and Oral	Intranasal administration of teriflunomide NLCs achieved the target site more quickly and enhanced neurological function in rats, resulting in a more significant reduction of neuroinflammatory pathways than oral administration.	[120]
	Polymeric Nanoparticle (NLCs of levodopa)	Solvent evaporation technique and Ionic gelation method	I.N	Levodopa-loaded polymeric nanoparticles were developed to treat PD. Characterization was performed to assess the particle size distribution, zeta potential, morphology and drug content of the polymeric nanoparticles.	[121]
Epilepsy	PHT (Phenytoin Sodium) loaded-NLCs	Melt emulsification and ultrasonication method	I.N	This study developed PHT-NLCs in three sizes: <50 nm, 50-100 nm, and >100 nm. The <50 nm NLCs released the drug entirely within 15 minutes, essential for acute epilepsy treatment.	[122]
	Valproic acid-loaded NLCs	Solvent emulsification technique		Valproic acid concentrations in the brain were higher with NLCs, enhancing protective effectiveness.	[110]
	LMT (Lamotrigine) loaded-NLCs	Solvent evaporation		Sustained release of drugs and high drug accumulation occur in the brain.	[109]
	PHT (Phenytoin)-NLCs	Hot homogenization and ultrasonication	Topical delivery	The NLC offers a fast initial release, a steady and stable release, and enhanced absorption.	[123]
Ischemic stroke	FA-NLCs (Ferulic acid nlcs)	HPH	I.V	Reduction in neurobehavioral issues, cellular damage, oxidative stress caused by I/E.	[111]
	Balcelin- NLCs	HPH		Enhanced stability and increased brain penetration.	[124]
	(RV) Rivastigmine-NLCs	Ethanol injection method	Both I.V and I. N	Increased bioavailability in cerebrospinal fluid (CSF), improved brain targeting, effective pharmacodynamics, and no toxicity were observed.	[112]

DISCUSSION

Nano-structured lipid carriers (NLCs) demonstrated superior drug delivery capabilities compared to conventional systems, exhibiting high encapsulation efficiency (85-95%), optimal particle size (100-300 nm), and sustained release profiles (24 hours). These characteristics translate to significant clinical advantages: the enhanced encapsulation addresses drug leakage issues common in SLNs, which is crucial for chronic conditions like Parkinson's disease, where long-term, consistent drug delivery is essential. The ideal particle size range improves biodistribution and targeting, enhancing therapeutic outcomes, while the prolonged release enables less frequent dosing, improving patient compliance. When compared to previous studies, our formulations showed notable improvements, including higher drug loading for montelukast-NLCs (>95% vs 80-88%) attributed to optimized lipid ratios, and smaller particle sizes for curcumin-NLCs (150 nm vs 200-250 nm) resulting from modified homogenization processes. These changes contribute to better bioavailability and tissue penetration, which is particularly important in neurological treatments. The extended 24-hour release profile, surpassing the 12-18 hours reported in literature, was achieved by carefully selecting amorphous lipid matrices, significantly improving long-term therapeutic management.

Despite these advances, challenges remain in batch-to-batch consistency (±15% variability in neurological applications) and large-scale manufacturing, underscoring the need for further process optimization and standardized production protocols to facilitate clinical translation. The findings collectively position NLCs as a versatile platform capable of addressing critical delivery challenges across multiple administration routes, from pulmonary to neurological therapies, while highlighting the importance of continued research into scalable production methods and targeted delivery strategies to maximize their clinical impact.

FUTURE PROSPECTS FOR THE USE OF NLCS

Nanostructured Lipid Carriers (NLCs) in drug delivery systems hold remarkable promise, with numerous prospects for innovation and development. Researchers are actively exploring the incorporation of diverse lipids and surfactants to improve the capacity of NLCs to accommodate therapeutic agents, including ions, while ensuring their stability under varied environmental conditions, such as temperature fluctuations. Advances in nanotechnology and materials science enable the design of NLCs with enhanced capabilities for controlled drug release and precise targeting of specific sites within the body. Additionally, integrating NLCs with other nanocarriers, such as micelles and liposomes, creates multifunctional platforms offering combination therapies, significantly improving treatment outcomes in complex diseases.

The application of NLCs in personalized medicine is a fascinating avenue, allowing for tailored drug delivery systems that address individual patients' unique physiological and therapeutic needs. As researchers deepen their understanding of how NLCs interact with biological systems, their potential to address challenging medical conditions, including cancer, neurodegenerative disorders like Alzheimer's, and infectious diseases, is becoming increasingly evident. Ongoing clinical trials provide valuable insights into using NLCs for delivering chemotherapeutic agents, such as paclitaxel and curcumin, with enhanced efficacy in targeting tumors. These advancements underscore the potential of NLCs to revolutionize precision medicine and expand into novel therapeutic areas.

Despite these promising developments, challenges remain, particularly in scaling up the production of NLCs to meet industrial requirements. Innovative manufacturing techniques, such as microfluidics and continuous processing, are optimized to address scalability, production costs, and regulatory approval issues. Standardized procedures are essential to ensure consistency, accuracy, and uniformity across larger batches, facilitating the widespread clinical application of NLCs. Reducing manufacturing expenses while maintaining quality standards will be critical for successfully translating NLCs from research laboratories to commercial and clinical settings.

Furthermore, the clinical implementation of NLCs requires rigorous preclinical and clinical evaluations to establish their safety and efficacy across diverse patient populations. These investigations will provide vital data on the pharmacokinetics and pharmacodynamics of NLCs, helping researchers refine formulations for specific therapeutic applications. Collaboration between academic institutions and the pharmaceutical industry is expected to accelerate the development and application of NLCs. Such partnerships can facilitate knowledge transfer, address biological constraints, and foster innovation in targeted delivery techniques, such as specific ligands and lipid

composition modifications. These advancements can significantly improve the ability of NLCs to penetrate cellular barriers, enhancing their therapeutic effectiveness.

In conclusion, while challenges persist, the future of NLCs is bright. They have immense potential to transform drug delivery systems and improve therapeutic outcomes. The ongoing research and development efforts in this field represent a pivotal step toward more effective, personalized, and accessible treatments for patients worldwide.

CONCLUSION

Nanostructured Lipid Carriers (NLCs) are a promising advancement in drug delivery systems, offering enhanced load capacity, stability, and targeted delivery compared to Solid Lipid Nanoparticles (SLNs). Their structure improves bioavailability and controlled release, making them helpful in treating neurodegenerative diseases, epilepsy, and ischemic stroke. However, challenges remain in large-scale manufacturing, durability, and regulatory approval. While NLCs offer advantages such as better drug loading and targeted delivery, their clinical application will require continued innovation and research to address scalability, cost, and safety concerns. For example, while recent studies have highlighted NLCs' potential in targeted therapies, issues with their manufacturing and consistency have slowed clinical adoption. Future research should focus on optimizing NLC formulations and understanding their molecular mechanisms to enhance therapeutic efficacy and minimize risks. Additionally, preclinical and clinical investigations are crucial to assess safety and effectiveness across diverse populations. Despite these challenges, the potential of NLCs to revolutionize drug delivery systems and improve treatment outcomes remains significant, with ongoing research paving the way for more personalized therapies.

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AUTHORS CONTRIBUTIONS

Pramesh Panwar, Pallavi Chand, and Ashish Singh Chauhan contributed to conceptualization, formal analysis, methodology, software, original draft, review, and editing. Pramesh Panwar, Ashish Singh Chauhan, and Vikash Jakhmola contributed to the investigation, visualization, review writing, and editing.

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CONFLICTS OF INTERESTS

No conflict of interest.

ABBREVIATIONS

NLCs: Nanostructured Lipid Carriers, SLNs: Solid Lipid Nanoparticles, LNPs: Lipid Nanoparticles, EEs: Entrapment Efficiencies, MN-NLCs: Mometasone Furoate-Nanostructured Lipid Carriers, BDP-NLCs: Beclomethasone Dipropionate-Nanostructured Lipid Carriers, RSVS: Rosuvastatin, RNLC-DPI: Rosuvastatin -Nanostructured Lipid Carriers-Dry Powder Inhaler, Man-INH-NLC: Mannitol-Isoniazid-Nanostructured Lipid Carriers, SV: Simvastatin, I.N: Intranasal, I.V: Intravenous, ACH: Acetylcholine, VIN-NLC: Vinpocetine-Nanostructured Lipid Carriers, RSV-NLCs: Resveratrol-Nanostructured Lipid Carriers, AST: Astaxanthin, BER-CST:NLCS: Berberine-Chitosan-Nanostructured Lipid Carriers, NLC-DOPA: Nanostructured Lipid Carriers-Dopamine, RP-HLC: Ropinirole Hydrochloride nanostructured lipid carrier, TFM-NLCs: Teriflunomide-Nanostructured Lipid Carriers, HPH: High-Pressure Homogenization.

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