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Nanostructured Lipid Carriers in Pulmonary Drug Delivery: Progress and Prospects

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Keywords

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Abstract

The potential of nanostructured lipid carriers to improve drug solubility, stability, and controlled release has made them a viable approach for pulmonary drug administration. Combining liquid and solid lipids, these carriers provide distinct benefits over conventional drug delivery methods, including enhanced bioavailability, less systemic adverse effects, and the capacity to encapsulate both hydrophilic and hydrophobic medications. In addition to delivering biologics, macromolecules, and cancer treatments, nanostructured lipid carriers may find use in the treatment of respiratory conditions such as asthma, chronic obstructive pulmonary disease, and pulmonary infections. Notwithstanding their benefits, there are still issues with manufacturing scaling up, getting beyond biological obstacles such mucociliary clearance, and handling safety and regulatory issues. More individualized, targeted care is becoming possible because to recent advancements in the design of nanostructured lipid carriers, such as smart delivery technologies and stimuli-responsive systems. This study emphasizes the potential of nanostructured lipid carriers to transform the treatment of respiratory disorders and enhance patient outcomes by highlighting their present advancements, difficulties, and future opportunities in pulmonary medication delivery.

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1. Introduction

Compared to traditional drug administration techniques, pulmonary drug delivery offers a number of benefits and has become a very successful approach for both local and systemic therapeutic treatments. The respiratory tract facilitates quick medication absorption and commencement of action because of its large surface area, thin alveolar epithelium, and abundant vascularization. This makes it very helpful in the treatment of respiratory conditions such lung infections, cystic fibrosis, asthma, and chronic obstructive pulmonary disease (COPD) [1]. Furthermore, by avoiding first-pass metabolism and gastrointestinal breakdown, pulmonary drug administration offers a viable method for systemic drug delivery, particularly for macromolecules like proteins, peptides, and nucleic acids. Nebulizers, metered-dose inhalers (MDIs), and dry powder inhalers (DPIs) are examples of traditional pulmonary medication delivery devices that have demonstrated significant efficacy in treating respiratory disorders. Nevertheless, despite their usefulness, these systems have a difficult time delivering drugs effectively. The challenge of focusing on certain respiratory tract areas is one significant drawback [2]. Particle size, flow rates, and breathing patterns are some of the variables that affect the deposition of inhaled particles in the highly dynamic respiratory system. While too-small particles may be expelled without settling in the lungs,

too-large particles frequently settle in the upper airways. This variation in medication deposition may enhance systemic adverse effects and decrease therapeutic effectiveness. The innate defensive systems of the lung present another difficulty for pulmonary medication administration. The respiratory system has developed defense mechanisms against infections, pollutants, and other foreign objects. Although alveolar macrophage activity and mucociliary clearance are essential for preserving lung homeostasis, they can also provide serious obstacles to medication administration. While macrophages can consume and remove nanoparticles, decreasing their bioavailability, mucus can retain drug particles, preventing them from penetrating deeper lung areas [3].

Furthermore, it is still difficult to achieve regulated and prolonged medication release in the lungs. In order to sustain therapeutic levels, conventional formulations sometimes need for frequent dosage, which can result in patient non-compliance and higher treatment expenses. Stability of the drug formulation is another concern, as many drugs, especially biologics, are prone to degradation during formulation, storage, and delivery. Additionally, some drugs may exhibit poor solubility or limited bioavailability when administered via inhalation, necessitating advanced formulation strategies to overcome these issues. Safety and biocompatibility are critical considerations in pulmonary drug delivery. The lungs are highly sensitive organs, and exposure to irritants or improper formulations can result in inflammation or toxicity. Regulatory challenges also exist, particularly for novel drug delivery systems that incorporate nanotechnology, which requires extensive evaluation of long-term safety and environmental impacts [4]. Despite these challenges, advancements in nanotechnology have opened new horizons in pulmonary drug delivery. By designing nanoscale carriers that can overcome biological barriers, improve drug stability, and enable targeted delivery, researchers aim to address many of the existing limitations. Among these developments, nanostructured lipid carriers (NLCs) have drawn a lot of interest because of their capacity to improve pulmonary absorption, offer regulated release, and encapsulate both hydrophilic and hydrophobic medications. These developments have the potential to transform the way respiratory illnesses are treated and increase the possibilities of pulmonary delivery for systemic treatments [5].

Nanotechnology has revolutionized drug delivery by enabling the design of nanoscale systems that address many challenges associated with conventional therapies. In pulmonary drug delivery, nanotechnology offers significant advantages, enhancing the efficacy and precision of treatments for respiratory and systemic diseases. Nanoscale systems, such as nanoparticles, NLCs, and liposomes, are uniquely suited for pulmonary applications due to their ability to penetrate deep into the respiratory tract [6]. Their small size, typically in the range of 1–100 nm, allows them to bypass mucociliary clearance and evade alveolar macrophages, ensuring prolonged retention in the lungs. Additionally, these systems can be engineered to optimize aerodynamic properties, enhancing deposition in specific regions of the respiratory tract. One of the key benefits of nanoscale systems is their capacity to improve drug solubility and stability. Many therapeutic agents, especially hydrophobic drugs and biologics, face challenges in achieving effective concentrations in the lungs. Nanocarriers can encapsulate these drugs, protecting them from degradation and delivering them in a controlled and sustained manner. This reduces dosing frequency and enhances patient compliance [7].

Additionally, by functionalizing carriers with ligands that attach to certain lung receptors, nanotechnology makes tailored medication delivery possible. This focused strategy improves treatment results and reduces off-target consequences. The argument for nanoscale devices in pulmonary applications is further supported by biocompatibility and less systemic toxicity. NLCs are a sophisticated type of lipid-based nanocarrier designed to overcome the drawbacks of conventional medication administration methods [8]. They have a special matrix structure because they are made up of a mixture of liquid and solid lipids that have been stabilized by surfactants. Because of the clear benefits this hybrid design offers over traditional lipid-based carriers, NLCs are especially well-suited for difficult applications like pulmonary medication administration. The enhanced ability of NLCs to load drugs is one of their distinguishing characteristics. NLCs include liquid lipids in their matrix, in contrast to solid lipid nanoparticles (SLNs), which are made entirely of solid lipids. Because of this addition, the solid lipids' crystalline structure is broken up, making room for more drug molecules. Additionally, its structural flexibility lowers the possibility of drug ejection during storage, which is a frequent problem with SLNs. Furthermore, NLCs may encapsulate hydrophilic and hydrophobic medications, expanding their use for a variety of medicinal substances [9].

Improved stability and controlled release characteristics are provided by NLCs. A prolonged medication release profile is offered by the solid-liquid lipid matrix, which is very helpful for long-term therapy of chronic respiratory disorders. To ensure effective delivery to the lungs, NLCs also increase drug solubility, shield delicate medications from deterioration, and make it easier for them to pass through biological barriers. NLCs provide a number of distinct benefits over other nanocarriers, such as liposomes and polymeric nanoparticles. Phospholipid bilayers make up liposomes, which work well for encapsulating drugs but have stability problems such oxidation and leaking [10]. NLCs, on the other hand, have better chemical and physical stability, which enables them to be used in a variety of environmental settings and stored for longer periods of time. Although polymeric nanoparticles provide exact control over medication release, their production frequently necessitates intricate and costly procedures. However, NLCs are more affordable for large-scale manufacturing since they may be made utilizing comparatively easy and scalable techniques like solvent evaporation or high-pressure homogenization. Safety and biocompatibility are two further advantages of NLCs. They are composed of lipids that are physiologically well-tolerated, reducing the risk of adverse reactions. This makes them particularly attractive for pulmonary applications, where the lungs‘ sensitivity to irritants necessitates the use of safe and non-toxic materials [11].

In pulmonary drug delivery, NLCs demonstrate superior performance by addressing the challenges of drug deposition, retention, and controlled release. Their ability to enhance aerosol properties, such as aerodynamic diameter and dispersibility, ensures effective delivery to targeted regions of the respiratory tract. Moreover, the functionalization of NLCs with ligands allows for receptor-mediated targeting, enabling precision therapy for conditions like lung cancer, infections, and chronic respiratory diseases [12].

2. Nanostructured Lipid Carriers

Advanced lipid-based nanocarriers, or NLCs, were created to get beyond the drawbacks of traditional delivery methods. Solid lipids, liquid lipids, and surfactants make up the three primary parts of their structure, and each one is essential to improving the system's performance, stability, and ability to load drugs. The NLC's core matrix is made out of the solid lipid component [13]. Glycerides, fatty acids, and waxes are examples of common solid lipids that stay solid at room temperature and body temperature. These lipids offer a strong structural foundation that aids in preserving the drug carrier's stability and regulating the encapsulated medication's release profile. The extremely crystalline structure of solid lipids alone, as in SLNs, restricts drug loading and raises the risk of drug ejection during storage [14]. NLCs add liquid lipids, such oils or unsaturated fatty acids, to the solid lipid matrix in order to get around this restriction. An amorphous or partly crystalline matrix is produced when liquid lipids break the crystalline structure of solid lipids. Over time, this disruption stops medicines from being expelled and improves the matrix's capacity to encapsulate a larger drug load [15]. Effective drug encapsulation and prolonged release are ensured by carefully balancing stability and flexibility through the ratio of solid to liquid lipids. The third component of NLCs, surfactants, lower surface tension and stop lipid nanoparticles from aggregating, stabilizing them. Bile salts, polysorbates, and lecithin are examples of common surfactants. By covering the lipid nanoparticles' surface, these surfactants guarantee colloidal stability and preserve the formulation's integrity throughout time. Surfactants can also affect the NLCs' physicochemical characteristics, including dispersibility, surface charge, and particle size. These three elements work together to create a nanocarrier system with improved stability and drug-loading capabilities. Both hydrophilic and hydrophobic medications can be efficiently encapsulated thanks to the spaces and flaws the solid-liquid lipid matrix produces in the crystalline structure. Additionally, the special matrix design minimizes dosage frequency and enhances therapeutic results by delivering a regulated and prolonged release of medications [16].

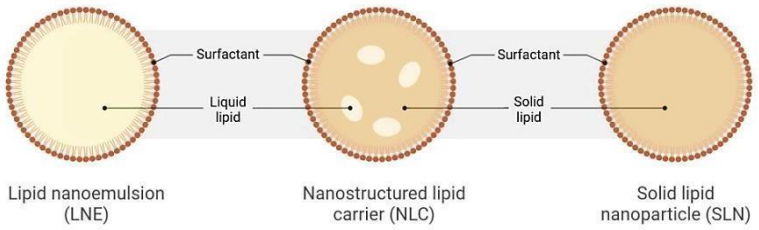

Figure 1: Types of Lipid Nanoparticles

2.1. Preparation Methods

NLCs are prepared using a number of tried-and-true methods, each specifically designed to produce the required stability, physicochemical characteristics, and drug-loading capabilities. The most often used processes are sonication, solvent evaporation, microemulsion, and high-pressure homogenization. The intricacy, scalability, and appropriateness of these methods for certain medication compositions vary [17].

2.1.1. High-Pressure Homogenization (HPH)

One of the most popular techniques for making NLCs, especially for large-scale manufacturing, is HPH. This method uses a high-pressure homogenizer to disperse a lipid phase in an aqueous surfactant solution at high pressures (100–2000 bar). Either high temperatures (hot HPH) or room temperature or below-room temperature (cold HPH) are used for the procedure [18]. The medication dissolves in the melting lipid phase, which includes both liquid and solid lipids, in the hot HPH technique. A pre-emulsion is then created by combining the melting lipid phase with a heated aqueous surfactant solution. To minimize particle size and create stable NLCs, this emulsion is repeatedly run through the homogenizer at high pressure. In contrast, cold HPH entails homogenizing the melted lipid and drug combination using an aqueous surfactant solution after freezing the mixture to solid lipid particles. Small, stable NLCs with good encapsulation efficiency are produced using both techniques [19].

2.1.2. Solvent Evaporation

Lipids and the medication are dissolved in an organic solvent, which is subsequently emulsified in an aqueous phase with surfactants, as the foundation of the solvent evaporation process. Lipid nanoparticles precipitate as a result of the organic solvent evaporating under lower pressure or ambient circumstances after the emulsion has formed. Because it doesn't involve high temperatures, this method works especially well for medications that are thermolabile. By modifying variables like stirring speed, surfactant concentration, and solvent type, it also enables improved control over particle size. However, leftover organic solvents could be dangerous and need to be purified further [20].

2.1.3. Microemulsion Technique

Lipids, water, and surfactants must combine to produce a thermodynamically stable system in order for the microemulsion process to work. Microemulsions can be utilized as precursors to NLCs and are spontaneously generated at particular compositions. At a temperature higher than its melting point, the lipid phase—which comprises both liquid and solid lipids—is combined with an aqueous surfactant solution. The lipids recrystallize, converting the microemulsion into a nanoparticulate dispersion of NLCs as it cools. Although this process is simple and repeatable, it is usually only used for small-scale manufacturing since it requires precise temperature control and certain compositions [21].

2.1.4. Sonication Technique

Another easy and efficient technique for creating NLCs is sonication. Using a probe or bath sonicator, the lipid phase is combined with the aqueous surfactant solution and exposed to ultrasonic waves. The ultrasonic energy breaks down the lipid droplets into smaller nanoparticles, creating a stable dispersion. Sonication is particularly useful for producing NLCs with narrow particle size distributions. However, excessive sonication can lead to particle aggregation or degradation of thermosensitive drugs, so optimization is essential [22].

Table 1: Overview of NLCs for Pulmonary Drug Delivery

S. No.	Types of NLCs	Drug	Method of Preparation	Application	References
1.	Solid Lipid NLCs	Rifampicin	High-pressure homogenization	Tuberculosis treatment	[23]
2.	Liquid Lipid NLCs	Salbutamol	Solvent emulsification	Management of asthma	[24], [25]
3.	Hybrid Lipid NLCs	Budesonide	Ultrasonication	COPD	[26], [27]
4.	Polymer-modified NLCs	Itraconazole	Microemulsion technique	Antifungal therapy	[28]

5.	Targeted NLCs with Ligands	Doxorubicin	Nanoprecipitation	Lung cancer treatment	[29]
6.	pH-sensitive NLCs	Voriconazole	Solvent diffusion	Pulmonary aspergillosis	[30], [31]
7.	PEGylated NLCs	Levofloxacin	Hot-melt emulsification	Bacterial infections in the lungs	[32], [33]
8.	Surface-modified NLCs	Amphotericin B	Double emulsion technique	Fungal infections in the respiratory system	[34]
9.	Stimuli-responsive NLCs	Paclitaxel	Solvent evaporation	Lung cancer chemotherapy	[35]
10.	Thermo-responsive NLCs	Ciprofloxacin	High-pressure homogenization	Pneumonia treatment	[36]
11.	Lipid-polymer hybrid NLCs	Beclomethasone	Coacervation	Asthma and COPD	[26], [37]
12.	Cationic NLCs	Albuterol	Emulsification-ultrasonication	Drug delivery to alveolar cells	[38]
13.	Ligand-conjugated NLCs	Erlotinib	Solvent injection	Targeted lung cancer therapy	[39]
14.	Mucoadhesive NLCs	Azithromycin	Solvent evaporation	Treatment of respiratory bacterial infections	[40], [41]
15.	Inhalable NLCs	Fluticasone propionate	Spray-drying	Pulmonary drug delivery for inflammation	[42], [43]
16.	Hydrophilic NLCs	Tobramycin	Freeze-drying	Treatment of cystic fibrosis	[44]
17.	Anionic NLCs	Clotrimazole	High-shear homogenization	Antifungal lung infections	[38], [45]
18.	Immuno-modulating NLCs	Curcumin	Solvent emulsification	Anti-inflammatory in pulmonary diseases	[46], [47]
19.	pH-sensitive NLCs	Piroxicam	Ultrasonication	Pulmonary delivery of NSAIDs	[30]
20.	Enzyme-responsive NLCs	Betamethasone	Hot-melt emulsification	Treatment of acute respiratory inflammation	[48], [49]
21.	Magnetic NLCs	Cisplatin	Magnetic stirring method	Targeted therapy in lung cancer	[50]
22.	Gold-coated NLCs	Resveratrol	Co-precipitation	Antioxidant therapy for lung conditions	[51]
23.	Core-shell NLCs	Methotrexate	Phase inversion	Lung cancer treatment	[28], [52]
24.	Oil-core NLCs	Indomethacin	Solvent diffusion	Pulmonary inflammation management	[53]
25.	Lipid-drug conjugated NLCs	Fenofibrate	Ultrasonication	Anti-inflammatory therapy	[26]
26.	Redox-sensitive NLCs	Gefitinib	Nanoprecipitation	Targeted lung cancer therapy	[54], [55]
27.	Biodegradable NLCs	Prednisolone	Hot-melt extrusion	Anti-inflammatory treatment	[56]
28.	Chitosan-coated NLCs	Ketoconazole	Double emulsion method	Fungal infections in the respiratory tract	[57]

29.	Charge-modified NLCs	Linezolid	Solvent injection	Bacterial infections in pulmonary diseases	[58]
30.	pH-triggered NLCs	Celecoxib	Spray-drying	Delivery of anti-inflammatory drugs	[54]

2.2 Critical Parameters in NLC Design

Important criteria including particle size, surface charge, crystallinity, and polymorphism have a big impact on the design of NLCs because they affect drug encapsulation, stability, release, and therapeutic efficacy. NLC performance is greatly influenced by particle size, especially when it comes to pulmonary medication delivery. NLCs can enter the pulmonary system deeply because of their usual size range of 50–500 nm. Because bigger particles may deposit in the upper airways and smaller ones run the danger of exhaling, an aerodynamic diameter of 1 to 5 μm is optimal for lung deposition in pulmonary applications [59]. Furthermore, smaller particles improve therapeutic results by providing a greater surface area for medication interaction and absorption. Particle stability and cellular interactions are impacted by surface charge, which is quantified as zeta potential. A stable colloidal system is ensured by a larger absolute zeta potential, either positive or negative, which inhibits particle aggregation by electrostatic repulsion [60]. Additionally, cellular uptake is influenced by surface charge; positively charged NLCs frequently show increased uptake as a result of interactions with negatively charged cell membranes. The lipid matrix's polymorphism and crystallinity are essential for the drug's ability to load and release. When liquid lipids are added to NLCs, the highly structured crystalline structure of the solid lipids is broken up, resulting in an amorphous matrix with fewer polymorphic transitions. This disruption improves encapsulation efficiency and reduces drug ejection. Additionally, the regulated and prolonged release of medications made possible by the amorphous or partly crystalline form of NLCs enhances therapeutic effectiveness and lowers the frequency of administration [61].

3. Advantages of NLCs for Pulmonary Drug Delivery

For pulmonary medication administration, NLCs provide a number of benefits that address important issues and improve therapeutic results. Their capacity to increase medication stability and solubility is one important advantage. NLCs provide extended stability by encasing hydrophilic and hydrophobic medications in their lipid matrix, shielding them from environmental influences and enzymatic breakdown. NLCs improve bioavailability by getting beyond the cellular and mucosal barriers in the lung. They can reach deeper areas of the respiratory system and break through the mucus layer because of their nanoscale size. NLCs can also avoid alveolar macrophages, which increases medication absorption and lengthens their retention period in the lungs. NLCs' regulated and prolonged release characteristics reduce medication concentration variations, which lowers dosage frequency and enhances patient compliance. They are especially appropriate for long-term respiratory disorders because of their lipid matrix, which permits a slow release of the medicine that is encapsulated [62].

Additionally, NLCs provide the possibility of tailored distribution by means of surface functionalization. via attaching ligands, such peptides or antibodies, to the surface of NLCs, certain cells or tissues, like cancer cells or inflammatory lung areas, may be targeted via receptors. NLCs exhibit excellent biocompatibility and safety. Composed of lipids naturally present in the body, they are non-toxic and well-tolerated, reducing the risk of adverse reactions and making them ideal for pulmonary applications. These advantages position NLCs as a promising tool for advanced pulmonary therapies [63].

4. Formulation Strategies for Pulmonary NLCs

4.1 Inhalation Formulations

Inhalation formulations of NLCs are designed for efficient pulmonary delivery using nebulizers, DPIs, or MDIs. Nebulizers are ideal for delivering liquid dispersions of NLCs, offering flexibility in dosing and suitability for a wide range of patients, including those with limited inhalation capacity. DPIs provide a dry, stable formulation with high patient convenience, requiring careful optimization of powder flow and dispersibility. MDIs, though widely used, require precise formulation with propellants for consistent delivery. Each device type demands tailored NLC formulations to ensure optimal aerosolization, lung deposition, and therapeutic efficacy [64].

4.2 Optimization of Aerosol Properties

Effective pulmonary delivery relies on optimizing aerosol properties of NLCs, particularly aerodynamic diameter and dispersibility. NLC particles should ideally have an aerodynamic diameter between 1–5 μm to reach the deeper regions of the lungs. This requires precise control of particle size, density, and shape during formulation. Interaction with lung surfactants is another critical factor, as surfactants facilitate particle dispersion and absorption in alveolar spaces. Tailoring NLCs to mimic or enhance surfactant interactions improves drug bioavailability, retention, and efficacy, ensuring therapeutic success in pulmonary applications [65].

4.3 Stability Challenges in Pulmonary Formulations

Pulmonary NLC formulations face significant stability challenges, including particle aggregation and degradation during storage. Factors like temperature fluctuations, freeze-thaw cycles, and moisture exposure can compromise the structural integrity of NLCs, reducing their effectiveness. Developing lyophilized or spray-dried powders and incorporating stabilizers like cryoprotectants can enhance storage stability. Addressing aggregation requires optimal surfactant concentrations and advanced formulation strategies to maintain colloidal stability. These measures are critical for ensuring long-term efficacy and reliable performance of pulmonary NLC formulations [66].

5. Applications of NLCs in Pulmonary Drug Delivery

5.1 Delivery of Antimicrobial Agents

The use of NLCs to deliver antimicrobial medicines to the lungs is growing, especially in the treatment of respiratory illnesses such pneumonia, TB, and other bacterial or fungal infections. Their capacity to encapsulate both hydrophilic and hydrophobic medications improves antimicrobial agents' solubility and stability, guaranteeing that they reach the intended locations in the lungs with greater bioavailability [67]. NLCs can overcome the challenges posed by the mucus barrier and alveolar macrophages, delivering drugs directly to infected areas. Furthermore, their sustained release properties help maintain therapeutic drug levels, which is essential for treating chronic respiratory infections. Targeted delivery through functionalization of NLCs with ligands specific to pathogen receptors can further enhance the selectivity and efficiency of antimicrobial therapy, reducing the risk of systemic side effects and promoting better patient outcomes in the management of pulmonary infections [68].

5.2 Treatment of Pulmonary Diseases

NLCs have a lot of potential for treating a number of respiratory conditions, including cystic fibrosis, COPD, and asthma. These diseases often require continuous or long-term drug delivery, and NLCs offer the advantage of controlled and sustained release, reducing dosing frequency and improving patient adherence. In asthma and COPD, [69]corticosteroids, bronchodilators, and anti-inflammatory agents encapsulated in NLCs can be effectively delivered to the lungs, ensuring targeted deposition and reduced systemic side effects . In cystic fibrosis, NLCs can be employed to deliver gene therapies or enzymes to restore normal lung function. Moreover, the ability of NLCs to bypass mucus barriers and penetrate deeper lung tissues increases the effectiveness of treatments, offering a more efficient approach to managing chronic respiratory conditions and improving overall lung health [70].

5.3 Delivery of Biologics and Macromolecules

For the pulmonary administration of biologics and macromolecules such proteins, peptides, and nucleic acids, NLCs are very beneficial, which are often difficult to administer via traditional routes due to their instability, poor bioavailability, and inability to cross biological barriers. By encapsulating these large, sensitive molecules in NLCs, they are protected from enzymatic degradation and environmental factors, ensuring their stability and efficient delivery to the lungs [71]. The small particle size and controlled release properties of NLCs enhance the absorption of these biologics at the alveolar level, offering a non-invasive alternative to injections. Furthermore, NLCs can be functionalized to target specific lung tissues, increasing the specificity of treatment for diseases such as lung cancer or genetic disorders like cystic fibrosis, where targeted gene therapies or protein-based treatments are essential for effective therapy [72].

5.4 Cancer Therapy

NLCs provide a cutting-edge method for targeted drug delivery in lung cancer treatment, guaranteeing that chemotherapeutic agents or other anti-cancer medications reach the lung's malignant regions directly. NLCs' tiny particle size makes it easier for them to enter tumor cells, and ligands may be added on their surface to target cancer cells only, limiting side effects and harm to healthy organs [73]. NLCs

offer a platform for combination therapeutic approaches by encapsulating a variety of anticancer medications, such as small compounds, biologics, and gene therapies. Furthermore, their sustained and controlled release profile ensures that drug concentrations are maintained over time, improving treatment efficacy and patient compliance. This targeted approach enhances the therapeutic index of anti-cancer drugs, making NLCs a promising tool for improving outcomes in lung cancer treatment [74].

6. Challenges and Limitations

Despite the promising potential of NLCs in pulmonary drug delivery, several challenges and limitations must be addressed for their successful application. One major technical challenge is the scale-up and reproducibility of NLC production. While laboratory-scale production using methods such as high-pressure homogenization or solvent evaporation can yield high-quality NLCs, translating these processes to industrial-scale production presents challenges. Ensuring consistency in particle size, drug encapsulation efficiency, and stability on a large scale is critical. Variations in formulation parameters or raw materials can lead to batch-to-batch inconsistencies, potentially affecting the performance of the final product. Biological barriers also pose significant obstacles to effective pulmonary drug delivery. The lungs are equipped with defense mechanisms such as mucociliary clearance and alveolar macrophages, which are designed to protect the body from foreign particles [75]. Mucociliary clearance expels inhaled particles from the respiratory tract, while alveolar macrophages engulf and eliminate potential threats. These mechanisms can hinder the deposition and retention of NLCs in the lungs, reducing their therapeutic efficacy. Strategies to enhance NLC stability and evasion of the immune system, such as surface modification and size optimization, are essential to overcome these biological barriers. Regulatory and safety considerations are also crucial in the development of NLC-based therapies. The biocompatibility and toxicity of NLCs must be thoroughly evaluated to avoid adverse reactions in patients [76]. Due to the unique properties of nanoparticles, concerns over long-term safety, such as potential accumulation in tissues, must be addressed. Moreover, the approval pathways for nanomedicines involve rigorous testing and regulatory scrutiny, which can be complex and time-consuming. Ensuring the safety and efficacy of NLCs is essential for their acceptance in clinical practice and regulatory approval [77].

7. Recent Progress in Research and Development

The field of pulmonary drug administration has greatly benefited from recent advancements in NLC research and development, with preclinical studies, clinical trials, and changes in NLC design demonstrating encouraging outcomes. Preclinical research has shed important light on the potential of NLCs for pulmonary medication delivery, especially when employing animal models. Numerous studies have shown that NLCs may effectively transport a variety of medicinal substances, such as corticosteroids, antibiotics, and anticancer medications, straight to the lungs. These studies have demonstrated how NLCs can increase drug solubility, decrease systemic adverse effects, and improve the stability and bioavailability of encapsulated medications. NLCs' benefits in overcoming biological barriers, such mucociliary clearance and alveolar macrophage activity, which are frequent obstacles in pulmonary drug administration, have also been demonstrated in animal models. Additionally, NLCs' prolonged release profile in animal models has demonstrated better therapeutic results, especially for long-term respiratory conditions including COPD and asthma [78].

In clinical trials, the application of NLCs in pulmonary drug delivery has seen steady progress. Several clinical studies have focused on the use of NLCs to deliver drugs for respiratory diseases, including asthma and pneumonia. These trials have demonstrated that NLCs are capable of improving lung deposition, bioavailability, and drug release rates compared to conventional delivery systems. Clinical trials evaluating the safety and efficacy of NLC-based formulations have generally reported favorable outcomes, with NLCs showing minimal toxicity and good biocompatibility in humans. However, challenges remain in optimizing the formulation for specific patient populations and in ensuring reproducibility across different settings. As a result, while early-phase clinical trials have been promising, larger and more comprehensive trials are necessary to fully assess the potential of NLCs in clinical practice. More sophisticated and accurate pulmonary drug delivery systems have been developed as a result of advancements in NLC design. The creation of stimulus-responsive NLCs, which are designed to release their drug payload in response to particular environmental stimuli like pH, temperature, or the presence of particular enzymes, is one of the major advancements. By guaranteeing that the therapeutic substance is delivered only when and where it is

required in the lung, this method enables more focused and controlled medication release, increasing treatment efficacy and reducing adverse effects. Stimuli-responsive NLCs have the potential to improve the accuracy of pulmonary treatments, especially in conditions where localized medication administration is essential, such as cystic fibrosis or lung cancer [79].

Another exciting development is the creation of smart delivery systems that incorporate real-time monitoring capabilities. These systems integrate sensors or imaging agents into the NLCs, allowing for the monitoring of drug release and distribution within the lungs. Real-time monitoring can provide valuable feedback during treatment, ensuring that the desired drug concentrations are achieved in the target tissues. This innovation is particularly beneficial in personalized medicine, where treatment regimens can be adjusted based on the real-time monitoring of therapeutic response. The combination of smart delivery systems with NLCs represents a significant step forward in improving the precision, safety, and effectiveness of pulmonary drug therapies [80].

8. Future Prospects and Directions

The future of NLCs in pulmonary drug delivery holds significant promise, particularly in the realm of personalized medicine. Precision drug delivery using NLCs could revolutionize treatment regimens by tailoring therapies to individual patients' needs. Because NLCs can encapsulate a wide range of pharmaceuticals and release them in a regulated manner, they may be made to react to certain biological markers, guaranteeing that treatments are delivered to the lungs exactly where and when they are required [81]. For patients with long-term respiratory diseases including asthma, COPD, or lung cancer, this strategy maximizes therapeutic results by enabling more effective therapies with fewer side effects. The merger of artificial intelligence (AI) with nanoinformatics is one of the emerging topics in the area that is pushing the limits of NLC technology. AI and machine learning algorithms can help in the optimization of NLC formulations by analyzing vast amounts of data to predict the ideal combination of lipids, surfactants, and drugs for specific pulmonary applications. Nanoinformatics is enabling the design of more efficient and targeted NLCs by providing insights into the behavior of nanomaterials and predicting their interactions with biological systems. These advancements could accelerate the development of more effective and customized NLC-based therapies [82]. NLCs must overcome a number of obstacles before they can be widely used in therapeutic settings. Bridging the gap between clinical application and laboratory research is one of the main challenges. For NLCs to be successfully translated from lab to bedside, production scaling, repeatability, and regulatory barriers must be addressed. To achieve widespread clinical deployment, it is also necessary to carefully control long-term safety and overcome biological hurdles including mucociliary and macrophage clearance. Notwithstanding these difficulties, current studies and technical developments indicate that NLCs will be crucial to pulmonary medication administration in the future [83].

Conclusion

NLCs represent a promising and versatile platform for advancing pulmonary drug delivery. Their unique properties, such as enhanced drug solubility, stability, and the ability to provide controlled, sustained release, offer significant advantages for treating a range of respiratory diseases, including asthma, COPD, and lung infections. The development of NLCs has also shown potential in the delivery of biologics, macromolecules, and even in cancer therapy, demonstrating their capacity for targeted and effective treatment. Challenges remain in the translation of NLC-based therapies from laboratory research to clinical practice. Issues related to scale-up production, stability, and overcoming biological barriers, such as mucociliary clearance and macrophage uptake, need to be addressed for broader adoption. Furthermore, ensuring the safety and biocompatibility of NLCs, while navigating regulatory pathways, remains crucial to their success in clinical applications. Looking ahead, the integration of emerging technologies, such as AI and nanoinformatics, offers exciting possibilities for optimizing NLC formulations, enabling personalized medicine, and improving treatment outcomes. While significant progress has been made, continued research and innovation are necessary to fully realize the potential of NLCs in pulmonary drug delivery, offering new therapeutic avenues for patients with chronic and complex pulmonary diseases.

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Author Contributions

M.D. conceptualized the review, conducted the primary literature search, and drafted the manuscript. **P.C.** contributed to the critical analysis of the literature, manuscript refinement, and final editing. Both authors approved the final version of the manuscript.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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