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REVIEW ARTICLE

Multifunctional Nanoparticles for Gene and Drug Co-delivery *via* the Pulmonary Route: Difficulties and Advancements

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Abstract: Pulmonary drug delivery systems are targeted therapies for respiratory conditions that deliver drugs directly to the lungs for increased bioavailability and faster action. The selection of the pulmonary route is based on its rapid absorption, which avoids the liver's first-pass metabolism. The approach involves studying how these nanoparticles help encapsulate drugs, shield them from deterioration, and improve their absorption into the lungs. These problems are being addressed by recent developments in improved targeting techniques, surface alterations, and particle size optimization, which are improving stability, release, and distribution. Inhalable dry powder formulations and nanocarriers for immunotherapy and gene therapy are also encouraging. Still, problems continue, including formulation stability, industrial scalability, lung toxicity, and patient compliance with breathing devices. The efficacy of PDDS will depend on resolving these issues with technologies such as Nano printing, combination therapy, and customized drugs. These developments are anticipated to result in more practical and successful pulmonary treatments for respiratory conditions with further research. The focus of this review is the solid lipid nanoparticles, dendrimers, liposomes, and DNA or mRNA approaches. These NPs help protect drugs from degradation, help encapsulate them, and improve lung penetration. This review discusses the nanoparticle and gene therapy for the treatment of PDDS.

Keywords: Gene therapy, stability, targeting techniques, liposomes, nanoparticles, nano printing.

1. INTRODUCTION

Pulmonary drug delivery (PDD) has drawn a lot of scientific interest. Avoiding systemic side effects, reducing pharmaceutical decomposition, increasing efficacy, decreasing dosage frequency, and enhancing patient compliance are all made possible by the PDD approach [1]. The development of nano therapeutics with a range of uses in lung disorders finds critical gaps in the current therapeutic protocol and enhances treatment safety and efficacy. The environmental exposure to chemicals, particulates, and pathogenic organisms to the lung [2]. Since targeted therapy employs nanoparticles for drug delivery systems has the potential to enhance treatment while reducing medication toxicity [3]. More thought must be given to pulmonary medicine distribution since it is a non-invasive way to deliver medications to the lungs [4]. The respiratory system is the primary site of contact with the environment; it acts as an entrance for both potential treatments and infectious agents like bacteria and viruses [5], and also for chronic conditions like asthma, cystic fibrosis, and COPD [6]. The scope of pulmonary drug delivery has been greatly expanded over the past few decades by developments in formulation techniques, inhaler technology, and aerosol science. These developments have made it possible to administer a variety of medicinal substances, including biologics, small chemicals, and macromolecules [7]. The lungs are the perfect place to administer drugs because of their intricate and incredibly effective structure [8]. Every component of the respiratory system, such as the alveolar area, upper airways, and conducting airways, plays a unique role in both breathing and drug deposition [9]. The enormous surface area (roughly 70-100 square meters) and close proximity to the pulmonary capillary network make the alveolar region particularly fascinating [10]. Numerous factors, such as the drug's physicochemical characteristics, particle size distribution, aerosol dynamics, and delivery device selection, influ-

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ence drug delivery to the lungs [11]. Since ancient cultures used herbal remedies and aromatic substances to treat respiratory disorders, inhalation therapy has been used [12]. The introduction of pressurized metered-dose inhalers (pMDIs) in the middle of the 20th century marked the beginning of the modern delivery of lung medications [13]. These devices are made to produce aerosols with the ideal particle size, usually between 1 and 5 micrometers, to guarantee effective drug deposition and deep lung penetration [14]. Furthermore, advanced adherence tracking and new opportunities for personalized treatment have been made possible by the development of digital interfaces and sensors in smart inhaler technologies [15]. To fully benefit from pulmonary drug delivery, certain issues must be resolved despite its promise [16], the requirement for exact dosage to prevent local toxicity, and the variation in breathing patterns among patients is a major area of concern [17]. Furthermore, particular excipients and manufacturing techniques are typically needed when developing medications for pulmonary delivery in order to guarantee stability, disposability, and bioavailability [18]. Pulmonary drug delivery devices are a transformative approach to drug administration because they combine the advantages of customized treatment, systemic drug delivery, and patient convenience [6]. Drug administration through the lungs has the potential to revolutionize the treatment of numerous illnesses and enhance patient outcomes and quality of life by overcoming current obstacles and utilizing state-of-the-art technologies [19]. Next-generation bronchial drug delivery systems with improved functionality and wider applications are being made possible by further research in fields like liposomal formulations, inhalable biologics, and nanotechnology [20]. Gene therapy is a new treatment approach that tries to fix or replace faulty genes causing lung diseases [21]. It can help reduce symptoms or even stop the disease from getting worse, especially in conditions like cystic fibrosis [22]. Researchers are still studying it, but it offers hope for long-term relief in people with chronic lung problems [23]. This manuscript is about novel approaches for the treatment of pulmonary disease.

2. PULMONARY ROUTE CHALLENGES

Quick and non-invasive drug administration makes perfect drug delivery [24], like physiological barriers, precise drug deposition, and alveolar macrophage particle clearance are obstacles [25]. To get over these obstacles, developments in technologies, formulations, and patient education are required [24]. The pulmonary route and challenges as mentioned in Fig. (**1**).

2.1. Limited Drug Deposition

Making sure that enough of the drug reaches the exact spot in the lungs where it is needed, limited drug deposition refers to the challenge of obtaining adequate amounts of a drug to the targeted site of action within the body, especially when targeting specific tissues or cells [26]. Poor drug solubility, quick systemic clearance, difficulty overcoming biological barriers (the blood-brain barrier, for example), problems with bioavailability, and absorption are some of the possible causes of this limitation [27].

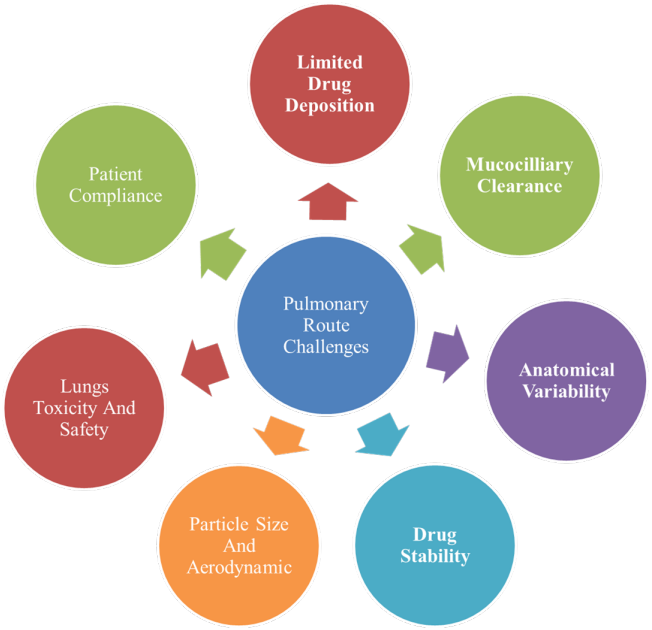

Fig. (1). Challenges associated with the pulmonary drug-delivery route. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.2. Mucociliary Clearance

Due to the lungs' natural capacity to filter out foreign substances, the drug may be quickly removed before it has an opportunity to fulfil its intended function [28]. Mucociliary clearance, a vital defence function of the respiratory system, purges the airways of germs, other debris, and inhaled particles [29]. This process promotes respiratory health by removing pollutants and lowering the chance of infection. Impaired mucociliary clearance, as seen in two respiratory conditions, cystic fibrosis and COPD conditions that can cause mucus accumulation and heightened susceptibility to infections [30].

2.3. Anatomical Variability

The medication may not be distributed uniformly because every person's lungs are unique, which could have unanticipated consequences [31]. The phrase "anatomical variability" refers to the inherent differences in the composition and arrangement of each person's body parts. Even while the majority of human anatomy follows a similar pattern, certain organs, veins, bones, or other components might differ in size, form, position, and even presence [32]. Understanding and accounting for these variations in radiography, surgery planning, and tailored medicine is crucial to enhancing patient outcomes and reducing complications [2].

2.4. Drug Stability

Drug stability refers to a medication's capacity to retain its therapeutic, chemical, physical, and microbiological qualities within predetermined parameters over the course of its shelf life [33]. It is essential to confirm that the medication is both safe and effective from the time of production until the expiration date [34]. To maintain the drug's potency, purity, and end-user safety, stability testing under varied environ-

mental conditions aids in determining the proper storage guidelines and shelf life [35].

2.5. Particle Size and Aerodynamic

Particle size and shape optimization are crucial for the physical properties that help the drug settle where it's needed and penetrate the lung tissue more deeply [11]. Their capacity to disperse, settle, and accumulate in the lungs is influenced by the size of the nanoparticles, which is typically measured in micrometres (μm) [36]. To help the drug bind where it's needed and penetrate the lung tissue more deeply [37].

3. PROGRESS IN NANOPARTICLE DRUG DELIVERY SYSTEMS

Nanoparticle-based drug delivery systems have revolutionized modern medicine by offering unprecedented precision in the treatment of numerous illnesses [38]. These systems use nano-scale carriers to deliver therapeutic compounds directly to target tissues or cells, as shown in Fig. (**2**). Liposomes, dendrimers, polymeric nanoparticles, and metallic nanoparticles, *etc*. [18].

3.1. Lipid-based Nano Carriers

Liposomes, lipid nanoparticles, and micelles are the three primary types of lipid-based nano-carriers used in medication and gene delivery applications. Liposomes, bilayer phospholipid vesicles, are frequently used to incorporate hydrophilic and hydrophobic drugs into the lipid bilayer, lengthen circulation duration, and improve capacity for lung localization [39]. Due to their exceptional biocompatibility, liposomes are more common expanded dramatically over the last 10 years, by producing a variety of novel liposomal formulations, including cationic liposomes, ribosomes, temperature-sensitive liposomes, and archaeosomes. There are currently just two FDA-approved liposomal formulations, despite these significant advancements at the bench: Marqibo, a liposomal vincristine sulphate injection for lymphoblastic leukaemia, and DOXIL, a liposomal doxorubicin injection for ovarian lung disease. Liposomes may be a promising drug and gene delivery system for the treatment of lung ailments [40]. Their lipid makeup is very similar to that of the natural cell membrane, which improves biocompatibility and lowers toxicity, two factors that are crucial for pulmonary administration when sensitive alveolar surfaces are involved. Additionally, because of their structural adaptability, a broad range of therapeutic agents, such as hydrophilic, hydrophobic, and amphiphilic medications, can be encapsulated, resulting in regulated release and enhanced stability of otherwise delicate substances [41]. The application of lipid-based nano carriers for targeted and prolonged drug release in conditions such as lung infections, asthma, and COPD, pulmonary medicine administration is particularly advantageous [42]. Recent advancements in surface modification of lipid-based nano carriers have enabled the inclusion of targeting ligands, which promote cellular absorption by lung epithelial cells and macrophages and aid receptor-mediated endocytosis [43]. Lipid-based nano carriers have demonstrated a novel method for treating hereditary and infectious lung diseases through transport of genes and siRNA [44]. In mouse models of lung disorders, studies showed the effectiveness of lipid-based nano carriers for gene transfer. 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) cholesterol was used in preclinical studies to successfully transport suppressor genes such as p53, TUSC2/FUS1, or mda-7/IL-24 to metastatic lung regions. This enhanced animal survival had a significant therapeutic impact [45]. DOTAP cholesterol nanoparticle technology, when supplied intravenously, was safe, well-tolerated, and free of treatment-related toxicity, according to the results of the phase A clinical trial. Additionally, the findings demonstrated that transgene and gene product expression took place, that the main and metastatic lungs effectively absorbed the nanoparticles, and that certain changes in their regulated signalling pathways were observed [46]. Additional phase I trials are being conducted to test DOTAP, and anticipated that pancreatic, ovarian, and breast cancers will be treated with cholesterol-based nanoparticle therapy. Which therapeutic genes are given will depend on the type of lung [47].

3.2. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are a type of lipid-based nano carrier made possible by drug delivery and encapsulation. They have a firm lipid core that is typically stabilized by detergents [48]. High biocompatibility, controlled release, and ability to encapsulate drugs enhanced drug loading, stability, biocompatibility, and ease of large-scale production. In order to achieve optical traceability, researchers recently used CdSe/ZnS quantum dots to encapsulate SLNs loaded with Bcl-2 siRNA and paclitaxel for synergistic combination therapy. All things considered, the characteristics of SLNs make them perfect for combining gene therapy, chemotherapy [49]. SLNs are ideal for treating respiratory disorders because they have improved drug targeting to the lungs, prolonged drug residence time, and lessened systemic side effects during pulmonary delivery [50].

3.3. Polymeric Nanoparticles

Polymers are used to create polymeric nanoparticles (PNP), as the name implies, biodegradable polymers like gelatin, albumin, chitosan, polycaprolactone, poly(lactic acid) (PLA), poly(lactic-co-glycolic) acid (PLGA), and polyalkyl-cyanoacrylates are widely used in recent years due to their subcellular size, biocompatibility, and controlled and sustained release characteristics [51] example, Patients not eligible for radiation treatment or curative surgery may benefited from first-line treatment with Abraxane, an in combination with carboplatin, an FDA-approved albumin-based nanoparticle containing paclitaxel is being used to treat locally progressed or metastatic non-small cell lung cancer. Several studies have shown that polymer nanoparticles improved the chemotherapeutic and radiotherapeutic effectiveness of lung disease medicines [52]. Increasingly acknowledged as cutting-edge pulmonary drug delivery vehicles, PNPs used their adaptable structure and functional properties to enhance the effectiveness of treatments for respiratory conditions [26]. Encapsulating a range of drugs, which includes proteins, nucleic acids, and tiny molecules. These nanoparticles are composed of chitosan and PLGA, which provide protection

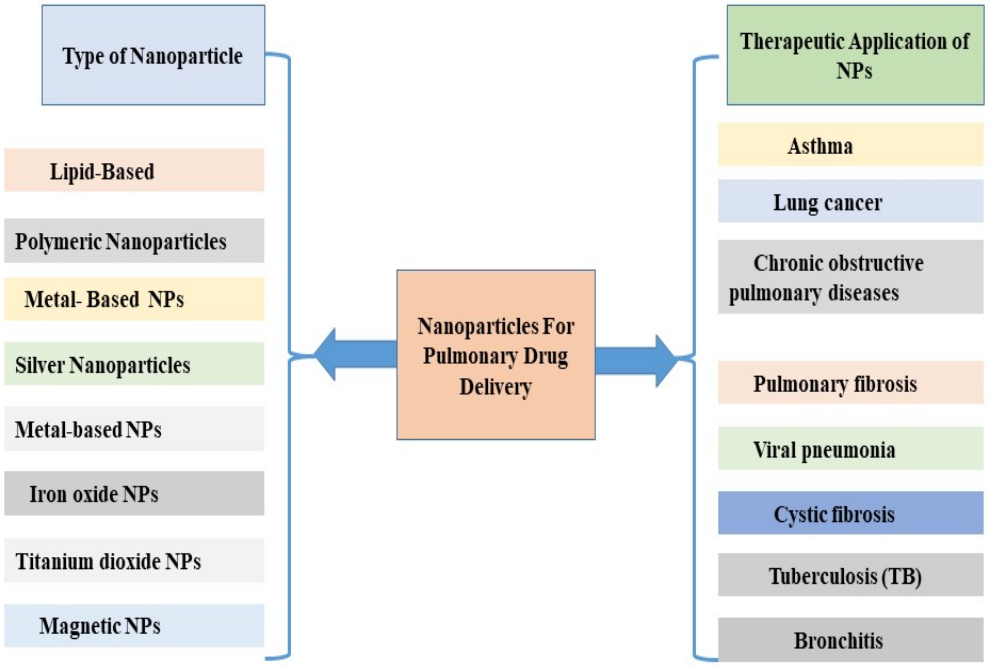

Fig. (2). Nanoparticle types for pulmonary drug delivery. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

against premature degradation and allow for controlled, prolonged release [53]. Because PNPs may be optimized for size, surface charge, and hydrophobicity to maximize aerodynamic qualities, allowing for deeper lung penetration and longer residence duration inside the alveolar region, they are especially well-suited for pulmonary delivery [2]. By enabling PNPs to bind particular cell receptors within the lungs, surface modifications like PEGylating or ligand conjugation improve pulmonary cell uptake and reduce off-target effects, enabling targeted delivery [54]. Site-specific drug administration greatly increased local therapeutic efficacy while lowering systemic exposure and potential side effects, making a focused strategy particularly beneficial in the management of chronic lung illnesses like asthma, COPD, and lung diseases [55]. Additionally, PNPs can be administered non-invasively, and increased patient compliance, using a variety of pulmonary devices, such as nebulizers and dry powder inhalers, *via* ensuring stability while being stored and uniform nanoparticle dispersion in breathing devices [56]. Currently, research focuses on enhancing these characteristics to make polymeric nanoparticles effective in the treatment of complex pulmonary illnesses. Asthma, COPD, cystic fibrosis, and other challenging lung diseases [57], because of their adaptable characteristics, PNPs can be loaded with immunomodulatory, bronchodilator, or anti-inflammatory drugs to treat inflammatory lung conditions as asthma and COPD. By limiting systemic exposure, it has focused delivery lowering the possibility of negative effects [58]. PNPs can better penetrate the thick mucus layer that characterizes cystic fibrosis by encapsulating antibiotics or mucolytic agents. This improves treatment outcomes by increasing medication availability to infection sites [2].

3.4. Hybrid Polymer Nanoparticles

Compared to unmodified nanoparticles, hybrid polymer nanoparticles (HPNP) made of PLGA and chitosan showed increased lung uptake and cytotoxicity in A549 cells. More importantly, the modified nanoparticles administered to a model of lung metastasis mice showed an increase in biodistribution localized to the lung [59]. Paclitaxel and STAT3 siRNA have also been effectively delivered using PLGA nanoparticles. In another study, PLGA nanoparticles loaded with paclitaxel and coated with anti-EGFR showed a significant binding affinity to cells that expressed EGFR in a mouse lung model [26]. Some hybrid nanoparticles were developed to optimize therapy outcomes for respiratory lung infections and even lung diseases [60]. To enhance structural stability and provide more controlled, extended release of pharmaceuticals, HPNPs blend polymers like PLGA with inorganic minerals like silica, iron oxide, or gold. Effective pulmonary treatment depends on this dual-material composition's ability to increase drug loading capacity, shield delicate medications from deterioration, and encourage deeper lung penetration [61]. Despite the immense potential of hybrid polymer nanoparticles, issues with regulatory approval, manufacturing scalability, and guaranteeing long-term safety and compatibility with lung tissue still exist [62]. Recent studies demonstrate that HPNPs not only enhance drug loading and aerosol performance but also allow tunable immunemodulating functionality, preserving lung epithelial integrity while minimizing pro-inflammatory responses — advances that bring them closer to safe inhalable therapies [63].

3.5. Metal-based Nanoparticles

Nanoparticles made up of metals, such as gold, silver, iron oxide, and zinc oxide nanoparticles, are increasingly

being studied in pulmonary medication administration because of their distinct physicochemical characteristics that allow targeted, controlled, and effective therapy of a range of lung illnesses [64]. Noble metals like gold and silver have been thoroughly studied for clinical uses, such as the detection and classification of lung illnesses and sensitive diagnostic imaging [65]. Gold nanoparticle-based biosensor technology was developed to detect lung diseases by analysing exhaled breath. The sensor combines various gold nanoparticle-based chemiresistors that use algorithms for pattern recognition. Furthermore, by tracking electrochemical signal probes of gold nanoparticle congregates, another research team reported employing an immunosensor to identify pictograms of enolase 1 (ENO1), an immunogenic antigen linked to non-small cell lung illnesses [63]. Gold particles have recently shown promising sensors for identifying and categorizing various lung disease types. The sensor could differentiate between SCLC and NSCLC, between normal and lung cells, and between two NSCLC subtypes [66].

3.6. Silver Nanoparticles

Because silver nanoparticles are highly antimicrobial, they may be utilized to treat bacterial lung infections, particularly those brought on by multidrug-resistant strains of the disease that cause tuberculosis and pneumonia [67]. Silver Nanoparticles (AgNPs) can effectively eliminate lung infections and lower the likelihood of systemic antibiotic resistance by releasing silver ions, which have a long-lasting antibacterial impact [68]. These nanoparticles can concentrate at particular lung regions when directed by an external magnetic field *via* improved localized delivery of medications or genes and reduced systemic exposure [69]. AgNPs can be added to inhaled formulations such as nebulizers or dry powders to enable targeted distribution to infected lung regions, thereby minimizing systemic exposure and negative effects [70]. In order to improve patient adherence, reduce dosage frequency, and increase efficacy, AgNPs can also be used in combination with other therapeutic treatments [71]. However, despite the obvious benefits of AgNPs, concerns have been raised regarding their potential cytotoxicity and oxidative stress on healthy lung cells, especially when used in greater amounts or for longer periods of time [72].

3.7. Metal Oxide Nanoparticles

Zinc oxide (ZnO) and other metal oxide nanoparticles are useful for administering medications to the lungs because of their antibacterial, anti-inflammatory, and biocompatible properties [73]. When treating chronic inflammatory diseases like asthma and COPD, ZnO nanoparticles can deliver anti-inflammatory medications to specific regions, enabling more localized care with less systemic damage [74]. The potential toxicity, long-term biocompatibility, and regulatory concerns of metal-based nanoparticles remain unresolved despite their superior pulmonary applications [75]. Now, researchers aim to make metal-based nanoparticles a powerful tool in pulmonary treatments by maximizing safety and effectiveness through surface chemistry and dose control [20]. Because of their inherent antibacterial and anti-inflammatory qualities, zinc oxide nanoparticles can be used to treat lung inflammation caused by COPD or asthma, as well as infections like tuberculosis [76]. ZnO nanoparticles can reduce systemic side effects by delivering therapeutic molecules directly to the lungs, improving drug absorption, and lowering the dosage required [77].

3.8. Iron Oxide Nanoparticles

Iron oxide nanoparticles offered a new approach to targeted pulmonary administration due to their magnetic properties. When directed by an external magnetic field, they can precisely target specific lung locations *via* increased medication concentration and reduced off-target exposure [70]. As targeted medications improved patient outcomes and treatment efficacy, beneficial for the treatment of pulmonary conditions [37].

3.9. Titanium Dioxide Nanoparticles

Titanium dioxide nanoparticles (TiO_2) are widely used in drug delivery due to their stability and photocatalytic properties [78]. But even with these encouraging uses, there are still issues with metal oxide nanoparticles' possible toxicity, like oxidative stress on lung tissue, and long-term safety in pulmonary use [79]. With the safe utilization of metal oxide nanoparticles for medicinal purposes and establishment as a novel solution in cutting-edge pulmonary drug delivery systems, researchers are actively investigating methods to alter surface characteristics and enhance biocompatibility [80].

3.10. Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) have been studied in great detail and used to diagnose and treat a variety of lung conditions. These are having a theranostic approach to help with both therapeutic agent delivery and imaging at the same time [81]. Nanoparticles of magnetic materials, including superparamagnetic iron oxide (SPIO), produce sub-lethal heat when exposed to alternating currents, which damages nearby tissues. The efficiency of lung cancer-targeted SPIO nanoparticles for the hyperthermic killing of NSCLC was assessed in a mouse model [82]. The growth of lung illnesses was considerably suppressed by the EGFR-targeted SPIO nanoparticles, which also demonstrated improved lung function retention [83]. Additionally, MNPs are being investigated for hyperthermia therapy, in which the particles produce localized heat under an alternate magnetic field, providing less invasive lung diseases destruction at the target site [84]. Furthermore, MNPs can be functionalized to transport antibiotics or anti-inflammatory medicines for infectious and inflammatory lung illnesses, including COPD and tuberculosis, enabling deep lung penetration and extended residence time [85]. MNPs' polymer coatings can be altered to increase drug stability and biocompatibility, which would make them more appropriate for pulmonary applications [86]. Currently, research is focused on maximizing the potential of MNP formulations, surface coatings, and targeting mechanisms to develop precise, high-tech pulmonary medications that minimize adverse effects and maximize therapeutic value [87].

3.11. Nanoparticles of Mesoporous Silica

The use of mesoporous silica (MSN) nanoparticles in pulmonary drug delivery systems has increased because of

their special structural characteristics, which include a large pore volume, a high surface area, and an adjustable pore size [88]. These nanoparticles permit the loading of a variety of substances, including proteins, nucleic acids, small molecules, and even vaccines, while shielding therapeutic components from the body's premature deterioration [89]. The high surface area of MSNs facilitates large drug adsorption, and their mesoporous structure can be designed to release the drug gradually or under control, resulting in longer-lasting therapeutic effects with fewer doses [90]. Their well-defined morphology and small size (usually between 50 and 200 nm) allow them to be efficiently transported past biological barriers like the mucus layer, which is a major obstacle to drug delivery to the deep lungs [91]. By surface functionalizing with targeting ligands or antibodies, MSNs can be directed to particular sites once they are inside the lungs, such as infection sites in pulmonary diseases or lung conditions [92]. By maximizing drug accumulation at the disease site and minimizing off-target effects, MSNs are highly beneficial in treating localized lung disorders, including lung diseases, asthma, COPD, and pulmonary infections [93]. Additionally, functional groups like PEG can easily be added to the surface of MSNs to improve their biocompatibility, reduce protein adsorption, and extend the time that they are in circulation [94]. The versatility of MSNs in drug delivery allows for the co-delivery of multiple medications, such as gene silencers and chemotherapeutic medications, providing a comprehensive approach to lung therapy or other complex lung issues [95]. The siRNA-carrying nanoparticle technique increased the therapeutic efficacy of doxorubicin and cisplatin by suppressing cellular resistance to the chemotherapeutics through the inhibition of targeted mRNA [96]. NSCLC cells that overexpressed EGFR were precisely targeted by MSNs modified with the cationic polymer polyethyleneimine and surface-attached with EGFR ligands [97].

The *in vivo* data showed that the tagged MSCs enhanced lung functions and decreased fibrosis symptoms in an animal model of bleomycin-induced pulmonary failure [98]. The primary target organ for Ag/TiO_2 nano hybrid toxicity and accumulation was still the original lung, which primarily showed up as pro-inflammatory and pro-fibrotic effects that warrant further attention [99]. A novel approach to MSC-related Idiopathic Pulmonary Fibrosis therapy offered a dual-functional platform for drug administration and cell image tracking [100]. Drug transport, encapsulation, antibacterial agents, plant growth-promoting agents, and plant protectors are among the uses of chitosan nanoparticles [101]. Lowering C5aR1 levels and blocking the activation of HMGB1/RAGE signalling and the production of EMT-related proteins, the C5aR1 inhibitor PMX205 significantly reduced the severity of lung fibrosis in mice exposed to SiNPs [102]. The particles' capacity to release the medicine continuously was validated by *in vitro* drug release tests conducted in a Trans well device [103]. Polydopamine Ziyuglycoside and Oseltamivir produced inflammatory mediators at significantly lower concentrations [104]. As investigations into novel alterations, nanotechnologies, and theranostic methods to enhance chitosan-based drug delivery systems persist, the future seems bright [105]. The use of pulmonary medications for various systemic disorders is increased by the current advancements and applications in pulmonary drug delivery for lung diseases [106]. NP-based drug delivery systems help to reduce adverse effects by requiring smaller doses and less frequent administration [107, 108]. Recent developments in the design, modes of action, and therapeutic uses of biomimetic vaccines have highlighted the significance in immunomodulation, targeted drug delivery, and personalized medicine [109, 110]. The effectiveness of lung-based drug delivery systems has increased due to technological developments in inhalation devices [111]. Many novel potential treatment approaches range of respiratory conditions that improve medication effectiveness and reduce adverse effects are documented [112]. Biodegradable Nanoparticles development and difficulties in using stimulus-responsive nanoparticles present new opportunities for the future [113, 114]. Some applications of nanoparticles in pulmonary drug delivery are mentioned in Table **1**.

4. RECENT ADVANCEMENT

Recent advancements in pulmonary drug delivery have been focused on nanoparticle (NP) technologies that enhance therapy delivery, targeting, and efficacy in the lungs in order to overcome the challenges of getting medications to this sensitive organ. Let's look into these specific areas of advancement:

4.1. Stimuli Responsive NP

Responsive to stimulus, pH, temperature, enzymes, and oxidative stress are some of the stimuli that NPs are made to respond to and are commonly observed in sick lung tissues [24]. When these NPs come into contact with the designated stimuli, they can change, enlarge, deteriorate, or release their drug cargo, ensuring precise, on-demand medicine delivery. Since the lung's sensitive environment and precise targeting make standard therapies challenging, these NPs hold considerable potential for the administration of pulmonary medications [115]. In response to stimulus, certain pathological markers, such as elevated reactive oxygen species (ROS) levels, disease-specific enzymes, or an acidic pH in inflammatory zones, can cause NPs to react in sick lung tissue [115]. By using different triggers, stimulus-responsive NPs can alter their structure, release kinetics, or drug-binding affinity, ensuring controlled and targeted medication release at the disease site [116]. pH-sensitive nanoparticles usually contain polymers that degrade or expand in acidic environments and release their therapeutic payload. These are particularly useful in treating inflammatory or tumorous diseases of the lungs since these tissues are generally more acidic than their healthy equivalents [117]. In comparison, redox-responsive NPs are made to react to increase ROS levels, a typical indicator of inflammatory lung illnesses such as cystic fibrosis and chronic (COPD), by releasing their therapeutic substance. Disulfide is present in ROS-responsive nanoparticles [2]. Another recent breakthrough is the emergence of dual- and multi-responsive NPs that respond to multiple triggers. NPs sensitive to both pH and ROS can provide even more precise control by requiring several conditions before releasing their drug content [118]. In order to enhance drug absorption and retention, stimuli-responsive (NPs) can be engineered to adhere to mucus for a short time and effectively transport the drug payload before being eliminated [24].

Table 1. Therapeutic application of different NPs in pulmonary drug delivery.

Type of Nanoparticles	Method of Formulation	Drug	Treatment Type	Outcome	References
Liposomes	Thin-film hydration	Budesonide	Asthma	Demonstrated outstanding anti-inflammatory and biosafety properties.	[98]
Gold nanoparticles	-	Methotrexate	Glioblastoma	Improved cell survival and post-transplant monitoring by shielding mesenchymal stem cells from oxidative stress and facilitating real-time CT imaging tracking in IPF therapy.	[99]
Polymeric nanoparticle	Solvent-evaporation method	Sparfloxacin and tacrolimus	Acute lung sepsis	Efficient antibacterial and anti-inflammatory treatments for sepsis brought on by lung infections, because they address inflammation in the condition.	[100]
Chitosan nanoparticles	Freeze drying	N-acetyl cysteine	Idiopathic pulmonary fibrosis	Enhanced medication release and antioxidant effects, and viable treatment for Idiopathic Pulmonary Fibrosis with better efficacy and prolonged circulation.	[101]
Iron oxide nanoparticles	Evaporate dry and milling	Dactinomycin	Lung cancer therapy	Exhibited improved delivery capabilities with chitosan coatings.	[102]
Dendrimers	Concertation	Erlotinib dexamethasone	Lung Cancer Chemotherapy, allergic asthma therapy	Focused on inflammatory cells in allergic asthma to produce quick and long-lasting anti-inflammatory effects.	[103]
Mesoporous silica	-	Polydopamine Ziyuglycoside and Oseltamivir	Viral pneumonia	Blocking the NLRP3 inflammasome pathway allows for quick viral removal and long-lasting anti-inflammatory benefits.	[104]
Carbon nanotubes	Normalization method	18β-Glycyrrhetinic	Lung inflammation and fibrosis	Reduced inflammatory markers and inhibited the signalling pathway.	[105]
Zinc oxide nanoparticles	Suspension method	NLRP3 inflammasome	Acute lung injury	Caused oxidative stress-induced mitochondrial damage and NLRP3 inflammasome activation.	[106]
Polycaprolactone nanoparticles	solvent evaporation	Ivermectin polycaprolactone	Pulmonary inflammatory disease	High entrapment efficiency and excellent pharmacokinetic characteristics, which greatly improved bioavailability and lung deposition.	[107]
Silver nanoparticles	Photo deposition method	Oropharyngeal aspirated	pulmonary fibrosis	Demonstrated strong pro-inflammatory and profibrotic effects.	[108]
Calcium phosphate nanoparticles	Precipitation method	Retinoic acid	Pulmonary fibrosis therapy	Co-delivering retinoic acid and microRNA during the therapy of idiopathic pulmonary fibrosis improved mesenchymal stem cell survival and permitted real-time imaging.	[109]
Albumin nanoparticles	Coacervation	benzothiazinone	Inhalation	Enhanced ability to combat M. tuberculosis both *in vivo* and *in vitro.*	[110]
PEGylated nanoparticles	Emulsion solvent evaporation	Iloprost, retinoic acid	Idiopathic pulmonary fibrosis	Improved the survival of mesenchymal stem cells and made real-time imaging tracking possible by enhanced cellular absorption and shielding.	[111]
Silica nanoparticles	Molecular dynamics method	C5a/C5aR1	Pulmonary fibrosis	Caused airway epithelial cells to undergo the epithelial-to-mesenchymal transition (EMT). Pulmonary fibrosis was considerably reduced by PMX205-induced C5aR1 inhibition, suggesting that the C5a/C5aR1 pathway.	[112]
Hydrogel Nanoparticles	Crosslinking method	Salbutamol sulphate	Asthma	Sustained therapeutic medication concentrations in the lung were improved by the notable delay in drug release.	[113]
Biodegradable nanoparticles	-	Ivermectin polycaprolactone	Pulmonary inflammatory diseases	Improved formulation showed decreased inflammatory mediators and increased lung accumulation.	[114]

Stimuli-responsive NPs are expected to be crucial in treating a variety of respiratory conditions with continued study, providing patients with individualized and incredibly successful treatment alternatives [119].

When treating lung cancer, immunoregulatory drugs or other anticancer therapies may work in concert with drug delivery techniques based on the tumor microenvironment or environmental stimuli [120]. Compared to Taxol, redox-responsive Paclitaxel dimeric NPs have a potential nano medicine for improved therapeutic efficacy against metastatic lung cancer [121]. Erlotinib possessed medication by released *via* disulphide cleavage [122]. Gemcitabine released in a simulated tumor microenvironment, the self-assembled sub-size (< 100 nm) (GSP NPs) with a significant loading capacity (24.6%) dramatically triggered apoptosis of B-cell lymphoma *in vitro* [123]. In another study, it was shown that cisplatin formulations, including polymeric nanoparticles, micelles, dendrimers, and liposomes, are more likely to provide cisplatin to the tumor over an extended period of time in response to changes in the tumor microenvironment [124]. Curcumin functionalized by adding different ligands to allow for intelligent targeting towards cancerous cells [125]. The fine particle dosage of Carboplatin was enhanced by the nebulized formulations, and showed that distribution to the lungs might be enhanced by using nano-carriers to increase its solubility. The aerosol properties of the Nano carriers were enhanced [126]. Studies on the safety profile, medication interactions, and significant clinical trials of berberine as found it effective in drug lung cancer treatment [127]. The most recent developments on 5-FU-loaded nano carriers have promised the cutting-edge cancer treatment tool [128]. In addition to quercetin treatments for lung cancer, we also benefit by using typical carriers of Nano drug delivery systems [129]. Gefitinib carrier systems reports based on nanotechnology, including silica, lipid, polymeric, and albumin nanoparticles for lung cancer treatment [130]. Adding to the systematic analysis indicates that adding neoadjuvant chemotherapy improved survival by 12% (1507 patients), which translates to a 5% increase in survival at 5 years [131]. Artemisinin and derivative nanoparticle formulations used for the treatment of cancer, malaria, and leishmaniosis [132] and synergistic medication combinations and the Co-administration of Sorafenib and other active ingredients Nano systems, including glypican-3, hyaluronic acid, apo lipoprotein peptide, folate, and superparamagnetic iron oxide nanoparticles demonstrated encouraging outcomes for focused therapy and other malignancies [133]. Vinorelbine decreased adverse effects and improved solubility [134]. Indirubin was observed as a GSH-sensitive medication [135]. Camptothecin released processed several stimulus-responsive as used to treat cancer [136]. The 3D spheroid investigation showed that CD-RES NPs had a stronger anticancer effect. All things considered, these results identified CD-RES NPs as a possible inhaled resveratrol delivery method for the treatment of NSCLC [137]. Thymoquinone improved solubility and precise lung targeting [138].

A list of synthetic bioactive compounds is shown in Table **2** and Fig. (**3**).

4.2. NPs for mRNA and Gene Editing Therapies

Gene-based treatments, particularly for hereditary illnesses like cystic fibrosis, target the lungs [139]. In order to provide localized and non-invasive therapy alternatives, NPs are promising vehicles for delivering mRNA and gene-editing materials (such as CRISPR-Cas9) directly to the lung cells. Lipid nanoparticles (LNPs) are a common option for mRNA distribution because of their capacity to encapsulate and shield mRNA, allowing it to be efficiently delivered into cells where it can generate therapeutic proteins. Common representations are in Fig. (**4**) [140].

The methods, *ex vivo* edited cell procedures, editing techniques that do not introduce genomic double-strand breaks, and access to airway basal cells [141]. Thymulin is a therapeutically effective gene therapy for long-term asthma [142]. PGA-co-PDL NPs have the potential to be used as a miR-146a delivery strategy for the treatment of COPD [143]. Pulmonary Arterial Hypertension reestablishing BMPR2 signalling specific to pulmonary endothelial cells [144]. CRISPR-Cas9 method for targeting treatments and personalized medicine in lung cancer, highlighting the significance of developing a delivery strategy in order to fully utilize the medication [145]. Gene therapy techniques used to create potent TB cures have the potential to completely transform therapeutic procedures [146]. Modified LNPs can help carry RNA therapies to the lungs and may pave the way for a novel pulmonary fibrosis treatment plan [147] and improved therapeutic outcomes, is focused on the inflammation-modulating NPs that alter the inflammatory cells, cytokines, and chemokines, and pneumonia microenvironments [148]. Most recent developments in the application of precision medicine to the diagnosis and treatment of adult viral pneumonia identify areas that require more investigation [149]. Lipid-polymer hybrid PNP nanoparticle system offers a novel approach to delivering mRNA and plasmid DNA while also having the capacity for long-term lyophilized preservation [150]. In mice and cotton rats, mRNA vaccine candidates expressing either native or prefusion-stabilized versions of RSV F protein produce strong neutralizing antibody responses that are comparable to those seen with an equivalent dosage of adjuvanted prefusion-stabilized RSV F protein [151]. The H1N1 influenza virus HA antigen-fused M2e peptide was loaded onto PDCD nanoparticles with mRNA to successfully induce M2e-specific antibodies and T cell immunological responses in vaccinated mice [152]. While gene therapy products are now available to treat certain disorders, like spinal muscular atrophy and hereditary retinal dystrophy, there are currently no effective treatment options for AATD-related pulmonary and, particularly, liver diseases [153, 154]. Many strategies supported the creation of innovative lung disease treatment solutions, providing patients with more effective and individualized treatment options [155]. Immunosuppressive medications like corticosteroids were reported to treat chronic HP, and antifibrotic therapy may be an option for patients whose condition worsens over time [156]. SC-based therapeutics for the treatment of smoking-induced disorders investigate the effects of smoking on SC biology and outline the mechanisms compromising SC-mediated repair mechanisms [157, 158]. Utero gene editing is a promising treatment and rescue strategy for monogenic lung diseases that are fatal at birth [159]. Bronchiolitis Obliterans syndrome (BOS), treated with targets

Table 2. Drugs and their mechanism of action are reported in the treatment of lung cancer.

Drug Name	Polymer Use	MOA	Diseases Type	References
Doxorubicin (DOX)	Smart stimuli-responsive carrier	Light/ultrasound/pH/enzyme-triggered targeted release	Lung cancer	[120]
Paclitaxel (PTX)	Redox-responsive dimeric nanoparticle	GSH/ROS-triggered medication release *via* disulfide cleavage	Metastatic lung cancer	[121]
Erlotinib	Lipid/polymer/inorganic carriers	EGFR inhibition due to Nano carrier-enhanced delivery	Lung cancer	[122]
Cisplatin	Polymeric NPs/micelles/dendrimers/liposomes	Long-term, stimuli-responsive medication release in the tumor microenvironment	Lung cancer	[123]
Docetaxel	Nano carriers (*e.g.*, liposomes, micelles, dendrimers	Targeting tumor cells improves bioavailability and overcomes P-gp efflux.	Non-small cell lung cancer (NSCLC)	[124]
Curcumin	Pluronic-chitosan (PF68-CS) + HA	Enhances pulmonary deposition and lung targeting through inhalation; increases solubility.	Lung cancer	[125]
Carboplatin	PCL-PEG-SS	Disulphide bonds are broken by GSH, which promotes release.	Small Cell Lung Cancer (SCLC)	[126]
Berberine	Smart polymeric nano-carriers	Targeted, stimuli-responsive administration using pH, light, enzymes, and ultrasound	Lung cancer	[127]
5-Fluorouracil (5-FU)	Lipid/polymer Nano carrier	The regulated release of stimuli	Lung cancer	[128]
Quercetin	Chitosan + Hallo site + GQDs	pH-sensitive managed release	Lung cancer	[129]
Gefitinib	Polymers, Liposomes, SLNs, NLCs, Albumin, Silica	An inhibitor of EGFR tyrosine kinase inhibits EGFR phosphorylation as which inhibits the growth of tumors.	Lung cancer	[130]
Mitomycin C	PLGA-SS-PEG	SS chain breakdown in tumor cells with elevated GSH	NSCLC	[131]
Artemisinin	(lipid, polymeric,	Improved absorption and solubility; focused administration; antileishmanial, anticancer, and antimalarial properties	Lung cancer	[132]
Sorafenib	Brush copolymer	Nano formulations decrease adverse effects and improve solubility.	NSCLC	[133]
Vinorelbine	Poly(β-amino ester)	A crucial element in the splitting of the cell's DNA after cell division is the microtubule.	NSCLC	[134]
Indirubin	PLGA-PEG	GSH-sensitive breakdown of disulfides for specific release	Lung adenocarcinoma	[135]
Camptothecin	Stimuli-responsive prodrug-based nanoparticles with activable linkers	Improved stability and decreased burst release with temporally tumor-targeted release through endogenous and exogenous stimuli	Lung cancer	[136]
Resveratrol	Polymeric nanoparticles filled with β-cyclodextrin and sulfobutylether	Increased cellular absorption and apoptosis through inhaled aerosol administration; enhanced solubility and stability	NSCLC	[137]
Thymoquinone	Various nanoformulations (*e.g.*, lipid, polymeric NPs)	Impacted on inflammation, tumors, and asthma through improved solubility and precise lung targeting	Lung disorders (*e.g.*, asthma, cancer,	[138]

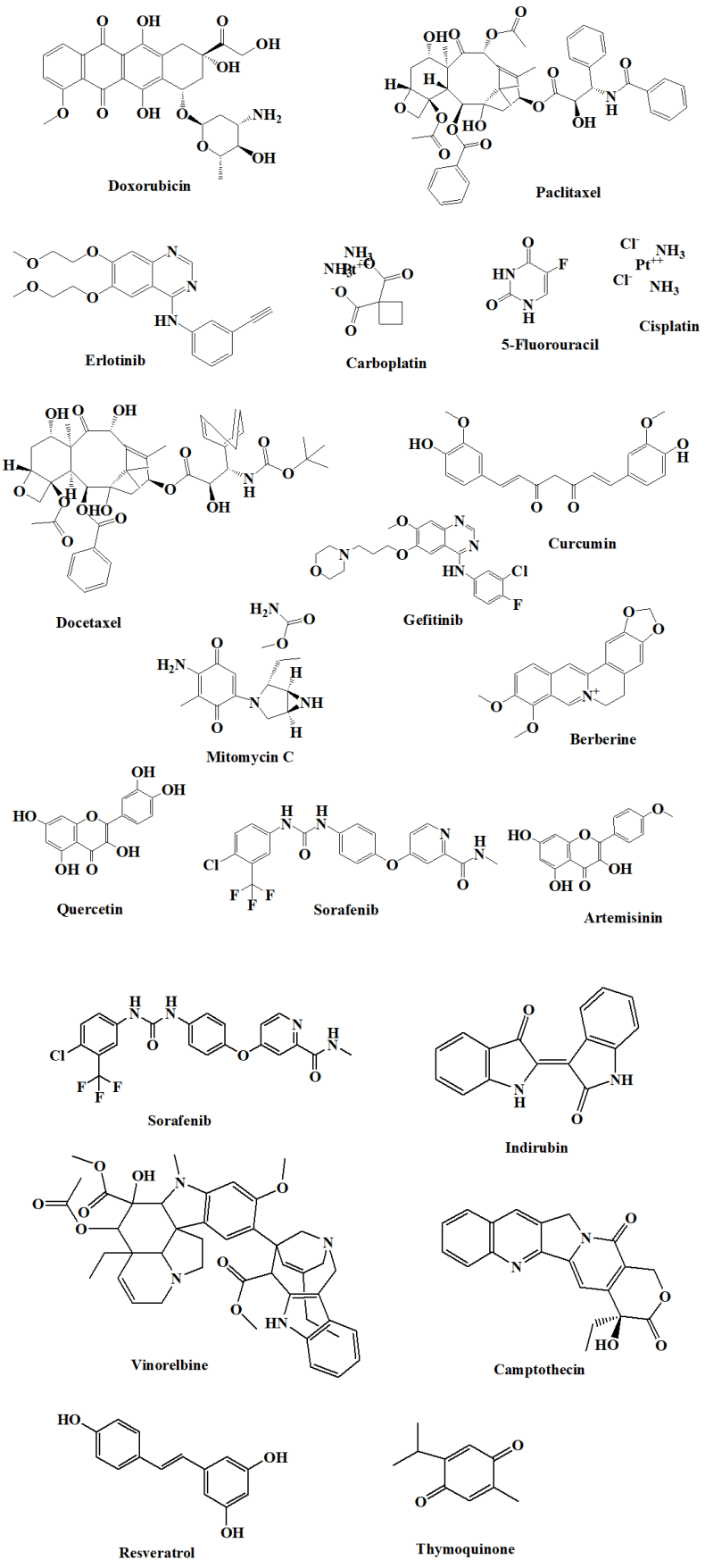

Fig. (3). Some compounds reported in PDDS.

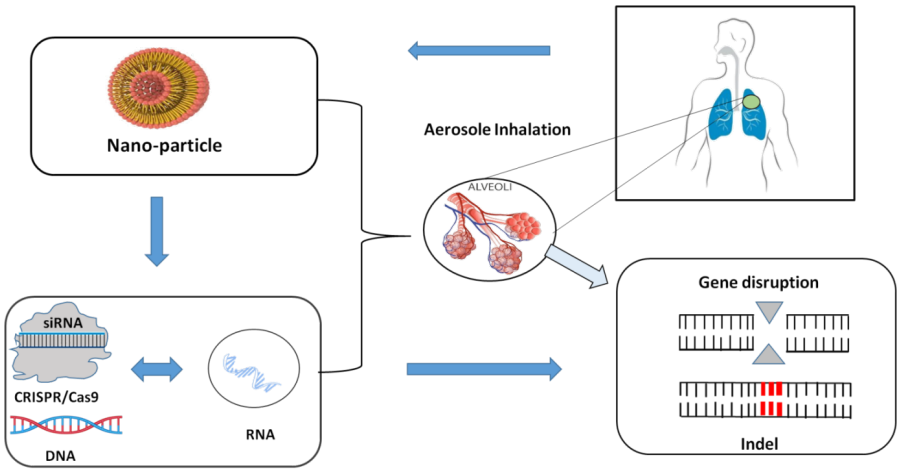

Fig. (4). Nano approaches involved in mRNA and gene editing therapies. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

under immune modulators, fibrosis-related genes [160]. Some NPs with genetic modification are reported for the pulmonary disease treatment [160-162], biosensors' capacity to accurately measure extravascular lung water accumulation and distinguish between hydrostatic and high permeability etiologies of pulmonary edema is highly valued by clinicians [163]. Human DNAI1 was expressed in the multiciliated cells of the pseudostratified columnar epithelia after mice were given a codon-optimized mRNA expressing DNAI1 and encapsulated in a lipid nanoparticle (LNP) by aerosolized inhalation [164]. Fluorescent nanoparticle imaging and an examination of PI3K inhibited in liver, spleen, and kidneys revealed minimal accumulation in these organs [165]. *Aspergillus*, a fungus that is common in the environment, can cause pulmonary syndromes and other diseases are treated with mRNA (drug-loaded NP therapy [166, 167]. Many diseases are reported to treat with DNA and miRNA approaches like pulmonary anthrax [168], pulmonary anthrax [169] hantavirus pulmonary syndrome [170], lung abscess [171], severe acute bronch [172], coccidioidomycosis [173], pneumoconiosis [174], avian influenza [175], middle east respiratory syndrome [176], whooping cough [177], cryptococcal meningitis [178],bronchopulmonary dysplasia [179], eosinophilic pneumonia [180], allergic bronchopulmonary aspergillosis [181], isolated pulmonary vasculitis [182], pulmonary langerhans cell histiocytosis [183], pulmonary hemorrhage syndromes [184], idiopathic pulmonary hemosiderosis [185], pulmonary eosinophilia [186], respiratory papillomatosis [187], pulmonary alveolar proteinosis [188], non-tuberculous mycobacterial lung disease [189]. Gene related to pulmonary disease treatment are discussed in Table **3**.

4.3. Enhanced Targeting

Because drugs must reach certain areas of the lungs without disturbing other areas, improved targeting is necessary for successful pulmonary drug delivery [190]. Diseases like lung disorders and asthma, this specific binding guarantees drug concentration at the site of illness, which is especially advantageous [191]. Recent developments have also examined magnetic and ultrasound-guided targeting, which target specific lung regions using external use [192]. Targeting ligands with compounds that preferentially bind to receptors or surface markers specific to diseased cells when designing NPs. These ligands can be small molecules, tamers, peptides, or antibodies [193]. When designing NPs, targeting ligands are substances that bind preferentially to receptors or surface markers unique to diseased cells [194]. Similarly, by utilizing ultrasonic waves to direct NPs to particular regions within the lungs, ultrasound-guided targeting makes transient holes in cell membranes that facilitate medication absorption [195]. These methods improved NP retention at the target site by reducing clearance of mucus and alveolar macrophages, which are commonly obstacles in the administration of pulmonary medications. Another exciting area is the development of environment-responsive targeting NPs, which only release their payload in reaction to disease-associated stimuli such as low pH, high ROS, or certain enzymes. For instance, NPs can be engineered to respond to elevated ROS levels in inflammatory lung diseases, limiting the delivery of medicine to the inflammatory areas. Because localized inflammation must be carefully managed to avoid harming good lung tissue, this enables more precise treatment of conditions like COPD [196].

Additionally, advancements in biomimetic NPs altered pulmonary targeting. NPs that "disguise" themselves as native cells can be created by researchers *via* coating them with lung-targeted or immune cell membranes [197]. These biomimetic NPs more successfully cross biological barriers, avoid immune detection, and more precisely target certain lung cells [198]. Since the immune system cannot stop the "cloaked" NPs from reaching pathogen-infected areas, this strategy has shown promise in the treatment of infectious disorders. By tackling issues with medication delivery specificity and reducing side effects, these targeting techniques are working together to create safer, more effective pulmonary treatments [2].

4.4. NPs for Prolonged Drug Release

In chronic lung diseases, therapeutic medication levels must be maintained over the long term. NPs designed by

Table 3. List of diseases and genes related to treating pulmonary disease.

Disease Name	TDDS	Gene Name/ mRNA	*In vitro*/*In vivo*	References
Cystic Fibrosis	CRISPR-loaded NPs	CFTR	*In vitro* (Human airway cells), *In vivo* (Mouse model)	[141]
Chronic Asthma	Mucus-penetrating NPs	Thymulin	*In vitro (Lung cells), In vivo* (Mouse)	[142]
Chronic Obstructive Pulmonary Disease (COPD)	PGA-co-PDL-DOTAP NPs (Cationic NPs)	miR-146a → IRAK1	*In vitro* (A549 cell line)	[143]
Pulmonary Arterial Hypertension (PAH)	Lipid Nanoparticles (LNPs)	BMPR2 mRNA	*In vivo* (Rat models: monocrotaline and SU5416-hypoxia)	[144]
Lung Cancer (NSCLC)	Lipid-based Nanoparticles (LNPs)	CRISPR-Cas9 (various targets)	*In vitro* and *In vivo* (preclinical tumor models)	[145]
Tuberculosis (Pulmonary TB)	Non-viral Nanoparticles (*e.g.*, lipid/polymer NPs)	Host genes *via* RNAi / CRISPR (*e.g.*, TLRs, autophagy-related genes)	*In vitro* (Macrophage cell lines), *In vivo* (Mouse models)	[146]
Pulmonary Fibrosis	Mannose-Modified Lipid Nanoparticles (LNPs)	siRNA targeting GTSE1	*In vivo* (Fibrosis animal models)	[147]
Pneumonia (Bacterial)	Inflammation-Modulating NPs	Anti-inflammatory targets (*e.g.*, cytokine/chemokine mRNAs)	*In vivo* (ALI/Pneumonia models)	[148]
Pneumonia (Viral)	Lipid Nanoparticles (LNPs) for precision gene delivery	Not specified (Precision Medicine Approach)	*In vivo* (Mouse models for respiratory viral infections)	[149]
COVID -19	Lipid-modified polymeric PNP NPs (L-PBAE + PLGA-PEG)	Spike-encoded plasmid DNA & mRNA	*In vitro* and *In vivo* (Mice)	[150]
Respiratory Syncytial Virus (RSV)	Chemically modified mRNA *via* LNPs (assumed standard for mRNA delivery)	mRNA encoding RSV Fusion (F) protein (prefusion-stabilized and native forms)	*In vivo* (Mice and Cotton Rats)	[151]
Influenza	Lipid-Polymer Hybrid Nanoparticles (LPP)	mRNA encoding HA antigen-fused M2e peptide	*In vitro* and *In vivo* (mice)	[152]
Alpha-1 Antitrypsin Deficiency	Lipid/Polymer-Based Nanoparticles	SERPINA1 gene (AAT gene)	*In vitro* and *In vivo* (mice)	[153]
Sarcoidosis	Lipid Nanoparticles / Polymeric NPs	mRNA targeting TNF-α or JAK/STAT pathway	*In vivo* (murine model)	[154]
Bronchiectasis	Nanomaterial-assisted (LNPs, Polymeric, Inorganic NPs)	CRISPR-Cas9 tools, synthetic biology circuits	*In vitro* and *in vivo* (general)	[155]
Hypersensitivity Pneumonitis	Nanoparticle-mediated gene modulation (exploratory stage)	Target: Inflammatory cytokines (*e.g.*, TNF-α, IL-2, IFN-γ)	*In vivo* (mice models; preclinical research)	[156]
Smoking-Induced Lung Injury COPD	MSC-loaded Nanoparticles (SC-NPs) or gene-activated NPs	Mesenchymal Stem Cells (MSCs) + Gene-activated therapy	*In vivo* (mouse/rabbit models of smoking-induced lung injury)	[157]
Occupational Lung Disease (Silicosis)	Inhalable polymeric/lipid NPs, MSC-loaded NPs	Inflammation-modulating genes, MSCs for tissue repair	*In vivo* (occupational exposure animal models); limited *in vitro*	[158]
Monogenic Lung Disease	In utero intra-amniotic CRISPR-Cas9 delivery *via* nanoparticles	SFTPC^I73T gene (targeted gene inactivation)	*In vivo* (mouse fetal model)	[159]

(Table 3) Contd….

Disease Name	TDDS	Gene Name/ mRNA	*In vitro*/*In vivo*	References
Bronchiolitis Obliterans	Nanoparticle-based immunomodulatory or gene therapy (under research)	Targets under investigation: immune modulators, fibrosis-related genes	Preclinical (animal models under exploration)	[160]
Lung Transplant Rejection	Liposomal aerosol nanoparticles (*e.g*., liposomal cyclosporine)	Immune modulation: cytokine suppression, immune-suppressant genes (*e.g*., sirolimus, cyclosporine pathways)	Clinical Trials (Human; n=39 trials analyzed)	[161]
Acute Respiratory Distress Syndrome (ARDS)	NP-enhanced genetically modified MSCs	Genetically engineered MSCs	Preclinical (mouse, rat models of ARDS)	[162]
Pulmonary Edema	Nanoparticle-based diagnostics (biosensors, quantum dots), gene-targeted delivery under study	Targets under study: inflammatory genes, aquaporins (AQP1), vascular permeability regulators	*In vivo* (Rat/Mice)	[163]
Primary Ciliary Dyskinesia	Lipid Nanoparticles (LNPs)	Codon-optimized mRNA for DNAI1	*In vivo* (Mice), aerosolized inhalation; ciliary beat frequency assessed	[164]
Lung Metastasis	Polymeric Nanoparticles (PNPs)	PI3K inhibitors	*In vivo* (Mice), fluorescence tracking, metastasis suppression study	[165]
Aspergillus Pulmonary Syndromes	Liposomal NPs, Polymeric NPs, Nanogels	Antifungal drugs (*e.g*., Amphotericin B, Voriconazole) delivered *via* NPs for Invasive and Allergic Aspergillosis	*In vivo* (Mouse/Rat Models); preclinical fungal lung infection models	[166]
Legionnaires' Disease	Lipid-based NPs, SLNs	No specific gene / mRNA (drug-loaded NP therapy)	Case reports, human retrospective data, and mouse models	[167]
Histoplasmosis	Liposomal NPs	No gene/mRNA used	Human clinical management	[168]
Pulmonary Anthrax	Not applicable	None (no gene/mRNA used)	*In vivo* (Guinea pig model)	[169]
Hantavirus Pulmonary Syndrome	siRNA (RNAi therapy)	siRNA targeting S, M, L segments of the HTNV genome	*In vitro* (Vero E6, HMVEC-L); *In vivo* (mice)	[170]
Lung Abscess	Not applicable	Not applicable	Clinical cross-sectional data	[171]
Severe Acute Bronchitis	Lipid Polymeric NP	Nanoparticles delivering anti-inflammatory agents or mRNA-based antivirals (under development)	Clinical Observation: retrospective human cohort study	[172]
Coccidioidomycosis	Lipid NPs, PLGA NPs	Antifungal drug delivery (*e.g*., Amphotericin B, fluconazole); vaccine antigens *via* mRNA/NPs	Mice model infected with *C. immitis*	[173]
Pneumoconiosis	Lipid Polymeric NPs	Anti-fibrotic agents (*e.g*., siRNA against TGF-β1, mRNA for anti-inflammatory cytokines)	Rodent model (mouse/rat) exposed to silica or coal dust	[174]
Avian Influenza (H5N1)	Lipid NPs / VLP-based NPs	mRNA encoding hemagglutinin (HA) antigens of H5 clade 2.3.4.4b virus	Mouse and ferret models for vaccine efficacy	[175]
MERS (Middle East Respiratory Syndrome)	Lipid Nanoparticles	mRNA encoding MERS-CoV Spike (S) protein	Mouse model (transgenic hDPP4 mice) for vaccine development and efficacy	[176]

(Table 3) Contd….

Disease Name	TDDS	Gene Name/ mRNA	*In vitro*/*In vivo*	References
Whooping Cough (Pertussis)	Lipid Nanoparticles	mRNA encoding Bordetella pertussis antigens (PT, FHA)	Mouse model for mRNA vaccine immunogenicity testing	[177]
Cryptococcal meningitis	Polymeric NPs / Lipid NPs	Nanocarrier-based delivery of antifungals (Amphotericin B, Flucytosine) or siRNA against fungal survival genes	Mouse model of *Cryptococcus neoformans* CNS infection	[178]
Bronchopulmonary Dysplasia	Lipid NPs / Exosome-based NPs	mRNA for VEGF, antioxidant enzymes (*e.g.*, SOD, catalase), or anti-inflammatory siRNA	Neonatal mouse model of hyperoxia-induced BPD	[179]
Eosinophilic Pneumonia	Lipid NPs, Polymer NPs	siRNA / mRNA targeting IL-5, IL-5R, Siglec-8, delivery of monoclonal antibodies like benralizumab	OVA-induced allergic asthma in mice	[180]
Allergic Bronchopulmonary Aspergillosis (ABPA)	Lipid NPs, Polymeric NPs, Biologics	siRNA targeting IL-5, IL-13, IgE; delivery of biologics like omalizumab (anti-IgE)	Aspergillus-sensitized mice model	[181]
Isolated Pulmonary Vasculitis	Lipid NPs, PEGylated NPs, PLGA NPs	siRNA targeting TNF-α / IL-6, endothelial repair mRNAs	Rat model of pulmonary vasculitis (monocrotaline-induced or surgically-induced)	[182]
Pulmonary Langerhans Cell Histiocytosis	Lipid NPs / PLGA NPs	BRAFV600E siRNA / MAP2K1 siRNA / MEK inhibitors	*In vivo* mouse model (CD11c-driven BRAFV600E transgenic)	[183]
Pulmonary Hemorrhage Syndromes	Liposomes / PLGA NPs	mRNA (hemostasis) / anti-inflammatory siRNA	*In vivo* (mice)	[184]
Idiopathic Pulmonary Hemosiderosis	Liposomal dexamethasone	Immunosuppressive therapy targeting inflammation / immune genes	*In vivo* (mice/rats) - Bleomycin- or LPS-induced lung injury model	[185]
Pulmonary Eosinophilia	Polymeric nanoparticles for IL-5 RNAi delivery	IL-5 / IL-5R pathway (*e.g.*, using siRNA or monoclonal antibodies like benralizumab)	*In vivo* (mice model of eosinophilic lung inflammation)	[186]
Respiratory Papillomatosis	Bevacizumab-loaded nanoparticles (VEGF inhibitor)	VEGF (angiogenesis suppression)	*In vivo* (mice) - Xenograft papilloma or orthotopic tumor models	[187]
Pulmonary Alveolar Proteinosis	GM-CSF-loaded nanoparticles / Liposomes	GM-CSF gene augmentation, GM-CSF receptor (CSF2RA/CSF2RB)	*In vivo* (mouse model of hereditary/autoimmune PAP)	[188]
Non-Tuberculous Mycobacterial Lung Disease (NTM)	Inhalable liposomes / polymeric NPs	Anti-mycobacterial drug-loaded NPs (*e.g.*, rifabutin, clarithromycin)	*In vivo* (mouse and guinea pig models)	[189]

providing a steady, regulated release of medications over several days or even weeks, prolonged drug release can lower dosage frequency and enhance patient compliance [26]. The polymers that degrade in these NPs, like PLGA, release the medication at a regulated pace and break down gradually in the lungs [199]. Long-term release NPs are ideal for treating chronic conditions like asthma and COPD because they reduce side effects by delivering the medication gradually rather than all at once [200].In order to manage chronic lung diseases like pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease, prolonged-release NPs are transforming the delivery of medications to the lungs by providing long-lasting therapeutic benefits [201]. By reducing the need for frequent dosages and ensuring a constant drug concentration at the desired location, this controlled, delayed release encourages patient compliance [1]. For instance, PLGA-based NPs provide extended drug delivery that is compatible with the treatment requirements of long-term respiratory therapy because they degrade over days or even weeks [199]. A new method for creating prolonged-release NPs is called core-shell design, in which a shell that dissolves at a regulated rate envelops a core NP containing the drug [202]. This is very useful for treating inflammation or infections that can occasionally recur in chronic diseases [203]. Moreover, mucoadhesive NP are being developed to adhere to the mucus layer and prolong the time that drugs

remain in the lungs [204]. Due to their coating with naturally sticky polymers like chitosan or hyaluronic acid, these NPs cannot be quickly removed by the lung's primary clearing mechanism, the mucociliary escalator [205]. In addition to prolonging medication retention, this mucoadhesion enhances absorption, resulting in a consistent therapeutic effect at lower dosages. Additionally, by encasing medications in a gel-like matrix that progressively breaks down in the lungs, hydrogel-based NPs are improving prolonged-release capabilities. Hydrogels are especially well-suited for respiratory applications because they offer an environment with a high water content that is comparable to lung tissue [206]. Their soft, flexible form reduces discomfort in delicate lung tissues, and they can be designed to break down and release medications over a range of timeframes, from days to months. Proteins, peptides, and other biologics are sometimes difficult to give because of their instability in the body, but hydrogel NPs are showing promise in delivering these substances [207]. When combined, these delayed drug release techniques are not only enhanced treatment but also lower the possibility of adverse effects linked to peak-and-valley dosing patterns, where drug concentration decline might result in decreased efficacy and spikes can cause toxicity [208]. Prolonged-release NPs are a crucial advancement for the treatment of chronic pulmonary disease and greatly enhance patient quality of life by sustaining a constant medication concentration and producing a more sustained therapeutic impact [26].

5. PDDS DOSE DELIVERY IN CHILDREN

Children most frequently utilize nebulizers, metered-dose inhalers (MDIs) with spacers, and dry powder inhalers (DPIs) [209]. Nebulizers are very useful for infants and major used because they don't require any specific coordination through a mask or mouthpiece; they turn liquid medication into a mist that the youngster inhales [210]. Whereas vibrating-mesh nebulizers, are quicker, quieter, and more efficient in delivering medication, both parents and children experience less stress during the process [211]. Little children cannot press and inhale at the same time, but MDIs are tiny canisters that release a precise quantity of medication. As a result, MDIs are typically used in combination with a holding chamber or spacer, which holds the drug in the air long enough for the child to breathe it properly [212]. Whether it is used with a mouthpiece for older children or a mask for younger ones, MDI with a spacer is quite effective and often works just as well as a nebulizer. Its portability and speed are further benefits [213]. Obstacles to pulmonary delivery in children include smaller airways, limited lung capacity, irregular breathing patterns, and resistance to using masks or other apparatus [214]. Crying or employing the incorrect technique can reduce the amount of medication that enters the lungs. Therefore, training and guidance are essential for both children and caregivers to ensure efficient utilization [215]. While choosing the ideal gadget, factors including age, ability, and the severity of the condition all come into play [216]. Therapy has become much easier, more effective, and more child-friendly thanks to innovations such as portable mesh nebulizers, soft-mist inhalers, and smart inhaler systems like using a smart nebulizer to better target small airways in children with severe asthma has been shown to substantially reduce exacerbations requiring oral corticosteroids [217].

6. CHALLENGES IN DRUG DELIVERY USING NANOPARTICLES IN LUNG DISEASE THERAPY

The recent decade has seen a considerable advancement in the utilization of nanoparticle systems in drug delivery technology. For diagnostic and disease monitoring applications, it is expected that further nanomedicine research will produce more sensitive and improved imaging agents as well as safe, practical, and efficient drug delivery. However, connecting quickly evolving innovative concepts and putting them into clinical reality presents many hurdles for nanomedicine research. It has always been difficult to create drug delivery systems using NP because they must have the right size to contain an efficient drug. Uncertain structure or shape, limited biocompatibility, an improper size distribution, and an inappropriate surface chemistry are all potential hazard elements in the biological environment. It is possible to create the perfect nanoparticle system for pulmonary medication delivery because of the differences in the particles' physicochemical characteristics and biological behaviour. NP systems will encounter a number of difficulties as they proceed through the preclinical and clinical testing phases, including immune response, rate of clearance from circulation, targeting effectiveness, and ability to penetrate past biological barriers. Having a solid understanding of how NP act biologically is crucial for achieving optimal drug delivery effectiveness. Identification of intracellular nanoparticle trafficking, aggregation tendencies, protein adsorption on nanoparticle surfaces, and particle-particle interaction in a biological context all depend on physicochemical property determination. Any of these factors can significantly change, leading to toxicology, loss of therapeutic efficacy, and/or insufficient drug delivery. As a result, the physicochemical characteristics of NP systems play a crucial role in determining their efficacy-toxicity balance. It is not advised to administer particles larger than 500 nm intravenously because of their quick elimination from the bloodstream. Additionally, by affixing particular ligands to their surface, nanoparticles can be actively targeted to enhance binding and interaction with the surfaces of the overexpressed protein receptors in the lungs. This strategy causes the medicine or gene to bind, get absorbed, and accumulate intracellularly in the targeted cells. However, the EPR effect may be primarily responsible for regulating the total accumulation and therapeutic efficacy of targeted nanoparticles. Furthermore, the complexity of nanoparticles and how they could affect medication delivery negatively needs to be further taken into account. In the realm of nanomedicine, multifunctional nanoparticles are popular subjects. Unlocking the full lung disease therapies will require addressing these issues through enhanced nanoparticle engineering, surface modification, and thorough clinical testing

7. FUTURE PROSPECTS

Novel applications for the diagnosis, detection, imaging, and therapy of lung diseases are constantly being developed, demonstrating the limitless promise of nanoparticle-based medicine. Nanoparticles are perfect for treating lung prob-

lems since they may be customized for a personalized medicine approach. Many experimental lung disease treatments based on nanoparticles use a combinatorial approach that balances the design of anti-lung disease drugs with targeting and monitoring moieties. The combinatorial method used in many experimental treatments for lung diseases based on nanoparticles balances the design of anti-lung disease drugs with the targeting and monitoring of moieties. Subtle changes to the complex's composition or manufacturing process altered its physical and/or chemical properties and can result in pharmacological and immunological issues. By effectively extending the circulation time, this strategy enhances the dispersion and accumulation of nanoparticles at the desired site. Challenge for researchers in immunological reactions brought on by nanoparticles, which can be brought on by the Nanocarrier, the payload, or both. In order to ensure perfect repeatability throughout the formulation process and minimize pharmacological and immunological challenges. In addition to the difficulties in creating and identifying nanoparticles, scientists also face the lack of standards in the study of nanomedicines, including production processes, functional testing, and safety evaluations. Similar to any new drug, therapy must overcome the following challenges: the best component and property design, repeatable manufacturing processes, the development of analytical techniques for sufficient characterization, favorable pharmacology and toxicity profiles, and evidence of safety and effectiveness from clinical trials. The pharmacological action of nanoparticles can be influenced by their complex composition, which includes several active components. Because of this intricacy, traditional pharmacokinetic, bioequivalence, and safety measuring testing must be modified. Regulatory bodies urgently require a comprehensive set of tests and a streamlined clearance process to proactively oversee the development of new products based on new technologies and expedite the delivery of nanomedicine to the clinic.

CONCLUSION

As discussed previously in the chapter, the pulmonary delivery system must administer a minimum therapeutic dose to the affected area in order to treat respiratory tract infections and achieve the desired therapeutic effect with the fewest possible side effects. Research is therefore required to understand not just the deposition process and the factors influencing it, but also the relationship between drug deposition and its pharmacokinetic behaviour after delivery. This has been accomplished by introducing physiologically based pharmacokinetic models to investigate the local concentration following deposition, the anticipated reaction, and the toxicological evaluation. The effective creation of new pulmonary delivery methods and new treatments would be aided by this type of modelling technique to better understand and study the system. Novel pulmonary delivery devices have significantly improved targeted distribution and delivery effectiveness to the lungs for respiratory illnesses. As the number of FDA-approved nano-particle delivery systems for various medical and diagnostic applications has grown, so too has research and development of these systems. The physiology and clearance process of the lungs can be thoroughly understood to help further design novel and more efficient nanoparticulate pulmonary delivery systems with higher levels of safety and efficacy. Consequently, substantial research is still required to bridge the gaps between laboratory and industrial formulation manufacturing in order to ensure the release of more advanced PDDS into the market to address the common respiratory illnesses.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: Study conception and design: ZN; reviewing and editing: KK and RD, Writing of manuscript: ST and MG; data collection: MRB; data analysis and result interpretation: YG. All authors reviewed and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AATD	=	Alpha-1 Antitrypsindeficiency
ABPA	=	Allergic Bronchopulmonary Aspergillosis
Ag/TiO_2	=	Silver/Titanium Dioxide
AgNPs	=	Silver Nanoparticles
ALI	=	Acute Lung Injury
AQP1	=	Aquaporin
ARDS	=	Acute Respiratory Distress Syndrome
BCL-2	=	B-cell Lymphoma 2
BMPR2	=	Bone Morphogenetic Protein Receptor Type 2
BMPR2 Mrna	=	Bone Morphogenetic Protein Receptor Type 2 Messenger Ribonucleic Acid
BOS	=	Bronchiolitis Obliterans Syndrome
BPD	=	Bronchopulmonary Dysplasia
BUD-LNPs	=	Budesonide-Loaded Liposomal Nanoparticles
C5aR1	=	Complement Component 5a Receptor 1
CD-MOFs'	=	Cyclodextrin-based Metal-Organic Frameworks
CD-RES NPs	=	Cyclodextrin-Resveratrol Nanoparticles
CdSe/ZnS	=	Cadmium Selenide/Zinc Sulfide
CFTR	=	Cystic Fibrosis Transmembrane Conductance Regulator
COPD	=	Chronic Obstructive Pulmonary Disease
COVID-19	=	Coronavirus Disease of 2019
CPAP	=	Continuous Positive Airway Pressure

CRISPR-Cas9 = Clustered Regularly Interspaced Short Palindromic Repeats-Cas9

CT = Computed Tomography

DNA = Deoxyribonucleic Acid

DNAI1 = Dynein Axonemal Intermediate Chain 1

DOTAP = 1,2-dioleoyl-3-trimethylammonium-propane

DOX = Doxorubicin

DOXIL = Doxorubicin Hydrochloride Liposome

DPIs = Dry Powder Inhalers

EGFR = Epidermal Growth Factor Receptor

EMT = Epithelial-mesenchymal Transition

ENO1 = Enolase 1

EPR = Enhanced Permeability and Retention

ETB = Endothelin B (ETB) Receptor

FDA = Food and Drug Administration

GFP = Green Fluorescence Protein

GM-CSF = Granulocyte-macrophage Colony-stimulating Factor

GQDs = Graphene Quantum Dots

GSH/ROS = Glutathione and Reactive Oxygen Species

GSP = Geometric Standard Deviation

H1N1 = Hemagglutinin Type 1 and Neuraminidase Type 1

HA = Hyaluronic Acid

HA/ M2e = Hemagglutinin/ Matrix 2 Protein Ectodomain

hDPP4 = Dipeptidyl Peptidase 4

HMGB1/RAGE = High Mobility Group Box 1/ Receptor for Advanced Glycation End-products

HMVEC-L = Human Lung Microvascular Endothelial Cells

HP = Hematoporphyrin

HPNPs = Hypersensitivity Pneumonitis

HTNV = Hantaan Virus

IFN-γ = Interferon-gamma

IL-2 = Interleukin-2

IPF = Idiopathic Pulmonary Fibrosis

IRAK1 = Interleukin-1 Receptor-associated Kinase 1

LC models = Lung-Central Pharmacokinetic Models

LD/ ED = Laser Diffraction/ Emitted Dose

LNP = Lipid Nanoparticle

LPP = Large Porous Particles

MAP2K1/ MEK = Mitogen-activated Protein Kinase Kinase 1

MERS = Middle East Respiratory Syndrome

MERS-CoV = Middle East Respiratory Syndrome Coronavirus Nanoparticles

MNP = Micro- and Nanoplastics

mRNA = Messenger Ribonucleic Acid

MSNs = Mesoporous Silica

NACN = acetylcysteine

NARDS = Neonatal Acute Respiratory Distress Syndrome

NLCs, = Nanostructured Lipid Carriers

NLRP3 = Nucleotide-binding Oligomerization Domain, Leucine Rich Repeat and Pyrin Domain Containing 3

NSCLC = Non-small Cell Lung Cancer

NTM = Non-tuberculous Mycobacterial

NTM-PD = Nontuberculous Mycobacterial Pulmonary Disease

PAH = Pulmonary Arterial Hypertension

PAP = Pulmonary alveolar proteinosis

PCL-PEG-SS = Poly(ε-caprolactone)-Poly(ethylene glycol)-disulfide Bond

PDCD = Pyruvate Dehydrogenase Complex Deficiency

PDDS = Pulmonary Drug Delivery System

PEI = Polyethylene Mine

PGA-co-PDL NPs = Poly(glycerol adipate-co-ω-pentadecalactone)

PLA = Poly Lactic Acid

PLGA-PEG = Poly(lactic-co-glycolic acid) - Polyethylene Glycol

pMDIs = Pressurized Metered-Dose Inhalers

PNPs = Polymeric Nanoparticles

PPI = Protein-Protein Interaction

PTX = Paclitaxel,

RNA = Ribonucleic Acid

ROS = Reactive Oxygen Species

SC = Subcutaneous

SCLC	=	Small Cell Lung Cancer
SERPINA1	=	Serpin Family A Member 1
SFTPB, SFTPC	=	Surfactant, Pulmonary-associated Protein B / Surfactant, Pulmonary-associated Protein C
SiNPs	=	Silica Nanoparticles
siRNA	=	Small Interfering RNA
SLNs	=	Solid Lipid Nanoparticles
SPIO	=	Superparamagnetic Iron Oxide
STAT3	=	Signal Transducer and Activator of Transcription 3
SWCNT	=	Single-walled Carbon Nanotube
TDDS	=	Transdermal Drugs Delivery System
TLRs	=	Toll-like Receptors
TNF-α	=	Tumor Necrosis Factor-alpha
TUSC2	=	Tumor Suppressor Candidate 2
VEGF	=	Vascular Endothelial Growth Factor
VLP-based NPs	=	Virus-Like Particle-based Nanoparticles
VRC	=	V Oriconazole
ZnO	=	Zinc Oxide

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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DECLARATION FOR AI USE

This is to confirm that no Artificial Intelligence (AI) tools were utilized in any aspect of the research, analysis, or writing process for the study.

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