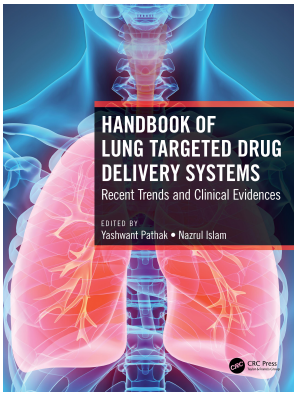

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

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Nanoparticle-Based Lung Drug Delivery: A Clinical Perspective

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Nanoparticle-Based Lung Drug Delivery: A Clinical Perspective

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47.1 Introduction

Lung diseases consist of wide variety of deadly and obstinate diseases, such as chronic obstructive pulmonary disease (COPD), asthma, lung cancer, idiopathic pulmonary fibrosis (IPF), and cystic fibrosis (CF) (1,2). Epidemiological data showcases the wide spread of these diseases, affecting a large group of people. About 300 million people globally are currently suffering from asthma, and 210 million people from COPD. Often the diseases are fatal and it is not possible to restore the lungs' capacity to their fullest (3,4). Lung drug delivery is challenging, primarily due to the lungs' defense mechanism against foreign particles. This mechanism prevents the drug particles from entering the respiratory tract also, removing and inactivating the settled particles out of the respiratory tracts (5). In addition, the mechanical, immunological, and chemical barriers play a major role in preventing drug particles from reaching their site of action. Mucus-producing and ciliated columnar epithelial cells, via mucociliary escalator system, mechanically remove the deposited insoluble particles (6). Immunological response is mounted by the macrophages in orchestra with the epithelial cells, T-cells, dendritic cells, and lymphocytes present in the alveoli (6). Chemically proteolytic enzymes and lung surfactants lead to inactivation and less adherence of the drug particles. Lastly, treatment success depends on the patient's adherence to the therapy and correct use of the therapy. These are some of the prominent problems faced by pharmaceutical companies; overcoming them will aid in achieving unmet clinical needs and leveraging the true potential of the pulmonary route (7–10). However, for chronic diseases, such as asthma and COPD, current pharmacotherapy only helps in symptomatic relief. Also, each patient needs to persevere with these drugs for a lifelong period (11). Furthermore, for lung cancer treatment, chemotherapy, radiotherapy, and surgery remain the preferred choices. The efficacy of new drugs depends on various aspects like deep lung deposition, ability to bypass mechanical (mucociliary escalation) and immunological barriers (macrophage clearance), and ultimately whether they are taken up in ample amounts by the target cells (12).

Traditionally, to treat chronic lung diseases, a variety of chemical entities, antibodies, peptides, and genetic molecules such as siRNA, miRNA, and shRNA have been used. Lung drug delivery to the site of action for the topically acting drugs and to the site of absorption for the systemically acting drug is itself a type of targeted drug delivery. The topically acting drugs offers several advantages, like rapid onset of effect, relatively low dose, and fewer side effects. Furthermore, for the systemically acting drugs, lungs provide an attractive target by virtue of the epithelial cells having >100 m^2 of area and <1 μm thickness (13).

In recent times, nano-sized carriers have shown promising results for lung disease pharmacotherapy by the virtue of their inherent physical properties. This platform technology is being used to improve pharmacokinetic properties of the currently available drugs, as well as in targeted therapy by using diverse targeting motifs. This approach helps to bypass limitations offered by the traditional therapy, including low diffusion and absorption, and inappropriate pharmacokinetic profiles (14,15). In gene therapy, the viral vectors have been shown to cause several side effects; on the other hand, nano-particulate based carriers have shown efficient delivery of the genetic materials with significant fewer adverse effects (16–19).

47.2 In Vivo Behavior of Nanoparticles

Nanoparticles, by virtue of their size, have a unique characteristic feature that is being leveraged for achieving disease-specific drug delivery. Their large surface area helps them interact with cells and surrounding tissue, enhancing their efficacy to a greater extent as compared to conventional dosage forms (20,21). In the conditions of tumor, chronic inflammation, and trauma there is an increase in blood flow, abnormal blood vessels, and high endothelial permeability, which helps the nanoparticles in accumulating at the disease-specific site (22–24). Based on these characteristics of cancer, nano-formulations such as Abraxane®, an FDA-approved anti-cancer agent for non small cell lung cancer, was developed (25). Similarly, liposomes of paclitaxel and cisplatin are in phase II clinical trials for lung cancer (26,27).

For other chronic lung diseases, like COPD and cystic fibrosis, in which low permeable blood vessels make it difficult for nanoparticles to accumulate and provide therapeutic effect, studies investigating the nanoparticles accumulating in

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different organ systems have shown low accumulation in the lungs as compared to other highly perfused organs systems. Therefore, for lung drug delivery, certain nanocarriers are not capable of improving the pharmacokinetic profile of the drug, but rather lead to toxicity. A specialized approach depending on the properties and type of nanoparticles is necessary, for instance, doxorubicin-loaded solid lipid nanoparticles and methotrexate-loaded albumin nanoparticles have high pulmonary distribution and efficacy (28,29). Solid lipid nanoparticles and liposomes are the most favored forms, considering the fact that they are less liable to aggregation (30). Surface modification with hydrophilic polymers and structural modifications of nanoparticles help in proper absorption and accumulation of drug particles in lungs (31). For instance, surface modified dendrimers with polyethylene glycol (PEG) lead to higher accumulation in the blood as compared to unmodified dendrimers, which showed minimal lung accumulation and were highly absorbed through the bloodstream (31). Various other determinants like size, patient-related factors, breathing problems, and methods of drug delivery need to be addressed for designing a disease-specific delivery method (30,32).

47.3 Drug Delivery System and Its Related Clinical Trials

Many clinical trials are filed on the ClinicalTrials.gov, a service of the United States Institute of Health. The database consists of various nanoparticle-based lung drug delivery clinical trials (Table 47.1). Here we discuss various nanocarrier-based drug delivery systems like polymeric, lipidic, hybrid lipid–polymer nanoparticles, dendrimeri, and Inorganic (Figure 47.1).

47.3.1 Polymer-Based Pulmonary Delivery

Polymers from natural or synthetic origin are widely used for nanoparticles formulations, and are being used to deliver chemotherapeutic agents, genes, or a combination of both to lungs. Polymers are repeated units of monomer, macromolecular in structure. They possess a key property of biodegradability, allowing their efficient and adverse-effect-free application. For instance, PEG polymer is extensively used for NP surface modification. Also, PEGylation of NPs, because of their biologically inert nature has led to a decrease in immune cell-mediated opsonization and deeper penetration in respiratory mucus cells (33,34). Gelatin-based NPs (GNPs) in combination with cisplatin for lung adenocarcinoma cells also enables deeper penetration into the lungs, thereby leading to higher accumulation and therapeutic efficacy (35). Furthermore, polymeric NPs have shown promising results as compared to viral vectors for delivery of genetic materials. The most widely used and studied polymer is polyethyleneimine (PEI), because of its electrostatic affinity it easily binds to nucleotides. Additionally, negatively charged phospholipids help in fusion of this positively charged polymer, facilitating the uptake and escape from endolysosomes (36). However, there have been reports of PEI-based toxicity, which can be overcome by the chitosan-PEI copolymer (37,38). To avoid drug resistance, combined delivery of genes and chemotherapy agents is being investigated, for example, doxorubicin-conjugated PEI linked by cis-aconitic anhydride with Bcl2 siRNA (39). Such characteristic properties of polymeric nanocarriers help in developing targeted and less toxic drug delivery for pulmonary diseases like asthma and tuberculosis.

47.3.2 Lipid Based Pulmonary Delivery

Lipid-based nanocarriers have been used from the dawn of nanobiotechnology and are composed of cholesterol and phosphotidylcholine (40). Liposomes are the key lipid-based NPs because of their ability to carry hydrophobic (lipophilic bilayer core) and hydrophilic drugs (aqueous core) (41). Liposomes with antibiotics, anti-cancer, antioxidant and anti-asthma drugs are being used for pulmonary diseases (42–45). For instance, liposomal 9-nitrocamptothecin (9NC) formulated with dilauroyl phospathidylcholine against lung cancer showed reduced drug load with the same effectiveness, which might lead to decrease in adverse effects (46). Furthermore, increased local lung deposition (310 ng/g) can be observed with liposomal camptothecin (CPT) as compared to conventional therapy (2 ng/g) (47). However, the systemic delivery of liposomal formulations tends to be eliminated by the reticuloendothelial system, limiting their application. On the other hand there is growing evidence of higher retention of liposomes when administered through inhalation.

Solid lipid nanoparticles (SLNs) have a solid lipid core in place of the liquid core of the droplet. A variety of materials are being used to formulate SLNs, like cholesterol (steroid), decanoic acid (fatty acid), tripalmitin (triglycerides), cetyl palmitate (waxes), and glyceryl behenate (partial glycerides) (48). However, the SLNs have several drawbacks, such as drug expulsion on storage and low drug loading capacity (49). Such challenges can be bypassed by the usage of nanostructured lipid carriers (NLCs), which consist of an unstructured solid lipid matrix and an aqueous phase comprising surfactant (50). Using sodium taurocholate as surfactant, and miglyol and compritol as unstructured solid lipid matrix, celecoxib-encapsulated NLCs were formulated for lung cancer treatment (51). The data showed a controlled drug release and higher therapeutic dosage reaching the target site.

47.3.3 Hybrid Lipid–Polymer Nanoparticles

Lipid-polymer hybrid nanoparticles (LPHNs) have a biodegradable polymer core and liposomal shell, with high loading capacity for both hydrophobic and hydrophilic drugs in polymeric and lipid core (52,53). A polymeric shell and lipid core has been used to decrease the lungs' clearance of the drugs via phagocytosis by macrophages. PEG5000–1,2-distearoyl-phosphatidylethanolamine (PEG5000-DSPE) loaded with paclitaxel was able to enhance the lung residence time, with 45-fold higher AUC as compared to I.V. administered drug (54). Hybrid nanoparticles can also be formulated using a hydrophilic polymer core and hydrophobic lipid shell. A 5-FU/poly-glutamic acid core and tripalmitin/cetylalcohol shell based lipid-coated NP showed prolonged release and higher lung accumulation of 5-FU as compared to polymeric microsphere and liposomes formulation (55).

TABLE 47.1

Various Nanoparticle-Based Clinical Trials for Lung Diseases (ClinicalTrials.gov)

Carrier Type	Drug	Clinical Trials ID	Description	Status
Liposome	9-Nitrocamptothecin	NCT00250068	To determine the overall response rate to liposomal 9-nitro-20(S)-camptothecin (L9NC) administered by aerosolization in patients with non small cell lung cancer (NSCLC).	Completed
Liposome	Amikacin	NCT03038178	To study efficacy, safety, and tolerability of once-daily dose of liposomal-amikacin for inhalation (LAI) for *Mycobacterium abscessus* lung disease.	Completed
Liposome	Cyclosporine	NCT01650545	To study efficacy and safety of aerosolized liposomal cyclosporine A in chronic rejection in lung transplant recipient with bronchiolitis obliterans syndrome (BOS).	Completed
Liposome	Cyclosporine A	NCT04107675	Safety in treatment of BOS1 in adult recipient of an allogeneic hematopoietic stem cell transplant.	Recruiting
Liposome	Paclitaxel	NCT02996214	Efficacy and safety of paclitaxel liposomes and cisplatin compared with gemcitabine and cisplatin for squamous NSCLC.	Active, not recruiting
Liposome	Gene therapy	NCT00004806	Efficacy and safety of lipid-mediated transfer of the cystic fibrosis transmembrane conductance regulator gene to nasal epithelium in patient with cystic fibrosis.	Completed
Lipid Nanoparticle	Biological: Quaratusugene ozeplasmid	NCT04486833	Safety and efficacy of GPX-001(a TUSC2, tumor suppressor gene, encapsulate by nonviral lipid nanoparticles) added to osimertinib in NSCLC patients with activating EGFR mutations.	Not yet recruiting
Micelles	Paclitaxel	NCT02667743	Paclitaxel micelles for injection and paclitaxel injection in combination with cisplatin for advanced NSCLC.	Active, not recruiting
Polymeric micelles	Paclitaxel	NCT01023347	Paclitaxel (Genexol®) and cisplatin versus paclitaxel loaded polymeric micelle (Genexol-PM®) and cisplatin in advanced NSCLC.	Completed
Albumin bound	Paclitaxel	NCT02016209	Platinum based albumin bound paclitaxel regimen in advanced NSCLC.	Unknown
Albumin bound	Carboplatin–nanoparticle albumin bound (Nab) paclitaxel	NCT04033354	HLX10 (recombinant anti-PD-1 humanized monoclonal antibody injection) + chemotherapy (carboplatin–nanoparticle albumin bound (Nab)-paclitaxel) for local or metastatic NSCLC.	Recruiting
Nanoparticles	Remdesivir and Neurosivir	NCT04480333	Safety, tolerability, and pharmacokinetics of inhaled nanoparticle formulation of remdesivir (GS-5734) and NA-831 (Neurosivir).	Recruiting
Nanoparticles	Docetaxel	NCT02283320	Docetaxel nanoparticles for injectable suspension for patients with KRAS positive or squamous cell NSCLC.	Completed
Nanoparticles	Docetaxel	NCT01792479	Docetaxel nanoparticles for injectable suspension for patients with NSCLC.	Completed
Nanoparticles	Hafnium oxide	NCT04505267	NBTXR3 and radiation therapy for treatment of inoperable recurrent NSCLC.	Not yet recruiting

47.3.4 Dendrimers-Based Pulmonary Delivery

Dendrimers are highly monodispersed nanoparticles with repeatedly branched molecules. Their surface and size can be controlled in a defined manner (56). Their added advantages are the ability to carry a high amount of drugs and high pulmonary absorption. For instance, PEG-modified dendrimers showed high absorption post inhalation (57). Various agents like antibiotics, steroids, and anti-cancer drugs are being delivered by dendrimers, to obtain enhanced and targeted therapeutics for chronic lung diseases (58–60).

47.3.5 Inorganic Nanocarrier-Based Pulmonary Delivery

Inorganic materials such as gold, silica, and iron oxide are widely used to make the nanoparticles, by the virtue of their plasmonic and magnetic properties. In particular, gold nanoparticles are being extensively investigated for gene therapy because their cationic metal ions are able to bind to anionic nucleic acids (61). Despite such advantages offered by inorganic nanoparticles, their application in pulmonary disease remains limited, as they tend to cause toxicity. Such metal NP-induced

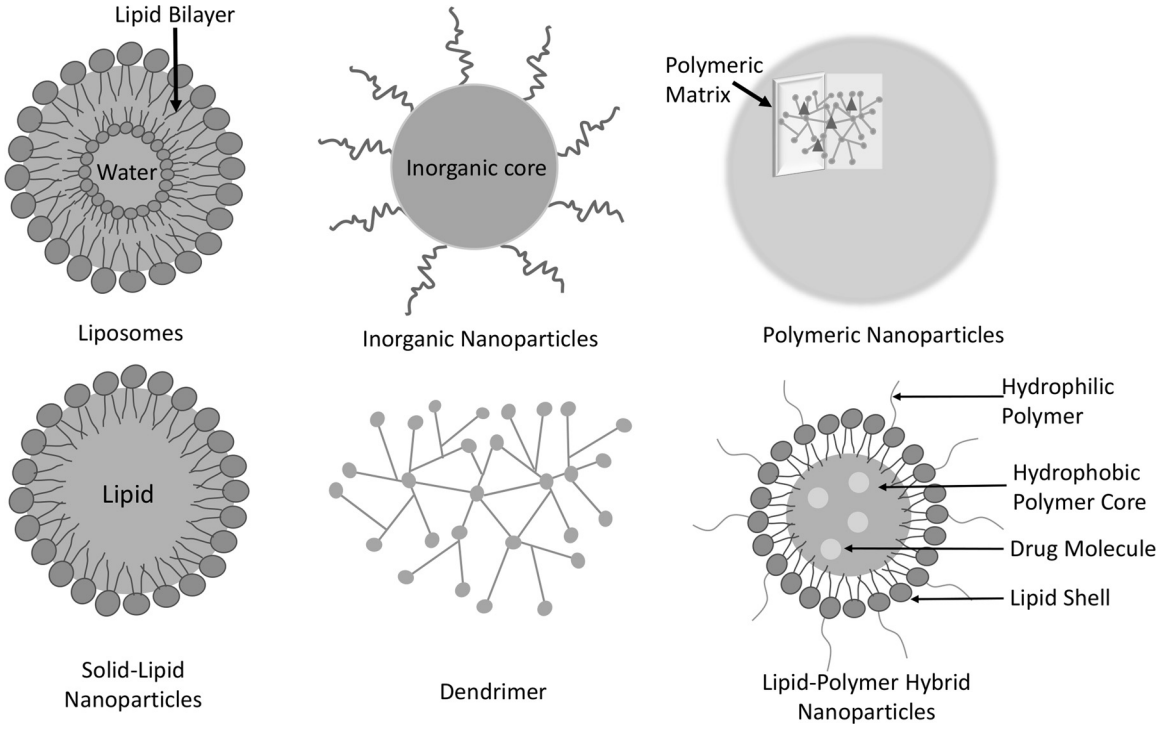

FIGURE 47.1 Sch ematic Representation of Various Nanoparticle-Based Drug Delivery System

toxicity can be controlled by regulating certain attributes like size, time, and concentration of metal ions used in formulating them (62). Additionally, they tend to form aggregates with serum proteins when given I.V. surface modification of these particles with PEG has been shown to reduce the aggregates' in formation (63). Magnetic NPs (MNPs) have emerged as a promising candidate for targeted drug delivery. Tumor ablation can be achieved through magnetic hyperthermia-generated heat. This can be achieved when an interchangeable magnetic field is applied to superparamagnetic iron oxide NPs (SPIONs) (64). Furthermore, mesoporous silica NPs (MSNs) are also used for target specific drug delivery, because of their large surface area and pore volume. The hydrophobic anti-cancer drugs can be entrapped into the pores or conjugated with electrostatic or covalent interaction with silicon groups, thereby protecting them from degradation (65,66). Quantum dots are semiconductors on a nonoscale, made up of group III-V or II-IV elements as a core and a polymer coating as a shell. Their lung retention time is higher, but can also cause cytotoxicity and oxidative stress in lung cells (53,67). Therefore, it is necessary to overcome their limitations and prove their safety before moving toward clinical trials of inorganic nanoparticles.

47.4 Factors Affecting the Toxicological Potential of Nanoparticles

Local deposition and accumulation of the insoluble nanocarriers and the response, such as increased inflammation, macrophages, and oxidative stress, has raised alarming safety concerns (68–70). A single dose of PEGylated poly-1-lysine dendrimer–DOX conjugate when given intra-tracheally caused severe toxicity and death in rats. It is thought to be due to dendrimer-led prolonged doxorubicin release in lungs. Also, the standardized tests need to be developed for membrane integrity, inflammatory mediator's release, and cell metabolic activity.

47.4.1 Shape and Structure

Shape and structure of the nanoparticles have severe implications for the toxicity profile of the nanoparticles. Different structures lead to varying toxicity profiles, for example, carbon black and graphite have different pulmonary effects as compared to carbon nanotubes (smaller structures with same composition). Likewise, fibrous nanoparticles have a tendency to cause granuloma formation and inflammation (71,72).

47.4.2 Particle Size

Inhaled nanoparticles tend to deposit in different areas of the respiratory pathway depending on their size. Larger particles get deposited on the upper respiratory tract, while smaller sized particles tend to get through the distal areas of the respiratory tract. For example, 20 nm diameter nanoparticles had 50% accumulation in alveolar areas, 15% in the nasopharyngeal area, and 15% in the tracheobronchial area (73,74). On the other hand, 1 nm diameter nanoparticles had 90% accumulation in the nasopharyngeal area and 10% in the tracheobronchial area (75). Nanoparticles, because of their large surface area teds to cause severe allergic reactions and cytotoxicity. Larger particles show relatively lower toxicity as compared to

particles of 100 nm in size or less, which tend to leak into organs and cause toxicity (71,76).

47.4.3 Surface Charge

Surface charge of the nanoparticles plays a key role in lung toxicity. Nanoparticles with positive surface charge lead to high toxicity as compared to negatively charged particles (77). For instance, the poly(styrene) nanoparticles with positive surface charge induced pulmonary inflammation and high total protein, cell recruitment, and lactate dehydrogenase release. However, no such reactions were observed with negatively charged counterparts of these formulations (78).

47.4.4 Biodegradability of the Nanoparticles

Biodegradable polymers are highly considered for the development of novel drug loaded nanoparticles, overcoming the limitations of inflammation caused by non-biodegradable nanoparticles (79,80). Dipalmitoylphosphatidylcholine (DPPC), a lung surfactant, is used to formulate nanoparticles, decreasing the toxicity by a significant amount. Amine modified branched polyester and linear PLGA biodegradable NPs, when compared to poly(styrene) nanoparticles, showed significantly lower inflammatory response. Furthermore, branched NPs, compared to PLGA, are preferable for frequently administered nanoformulations owing to their biodegradability profile (81).

47.5 Future Perspective and Concluding Remarks

In the recent past, various types of nano-formulation-based lung drug delivery have been developed based on different platform technologies. Novel therapies thus developed are promising candidates for their application in chronic lung diseases with antibodies, nucleic acids, chemotherapeutics, and combinatorial therapies. Alveofact® was the first FDA-approved liposomal formulation for respiratory disease (82). Liposomes are easy to scale up, devoid of irritation, and are biodegradable, making them a prominent candidate for lung drug delivery. Other liposome-based products like Pulmaquin® and Arikace® are under clinical investigation (83). A clinical trial of 9-nitro-20-camphothecin (9NC) with dilauroyl phosphatidylcholine (DLPC) liposomes was performed in 24 patients. Grade 1 or 2 based side effects were observed, with nausea, fatigue, and cough being the most frequent. Thus, concluded the study, safety of the liposomal formulations needs to be checked (84). Similar toxicity was observed in cholesterol- and DPPC-based liposomes loaded with cisplatin in 17 patients with pulmonary carcinoma (85). In the case of cystic fibrosis, highly viscous sputum is secreted that prevents the deposition of nanoparticles on the pulmonary epithelial cells. To tackle this situation, strategies such as surface shielding by PEG, encapsulation of mucolytic agents, and mannitol-based osmotic modification have resulted in increased drug penetration (86–88). Nanotoxicology and especially inorganic nanoparticle-related toxicity, inflammation, and immunogenicity need to be addressed (89). Although in vivo toxicity profile prediction of nanoparticles is hard, optimization and appropriate selection of nanoparticles might help bridge the gap between safety and attractive therapeutic function. Despite the fact that current clinical application of nanocarriers is limited in pulmonary disease, innovative nanomaterials are warranted.

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