

Liposome-Based Nanoparticle Delivery Systems for Lung Diseases: Opportunities and Challenges

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Abstract: The role of the lungs as one of the most important organs in the body cannot be overstated. When disease occurs in the lungs, due to the special physiological structure and barriers of the lungs, many drugs is often required to maintain the required blood concentration, which brings unbearable adverse drug reactions to the patients, reduces the tolerance of the patients to the drugs, and affects the effect of disease treatment. As a mature delivery system, liposomes are widely used in major fields, and more importantly, liposome-delivered drugs have been utilized in clinical treatments, effectively reducing the side effects of drugs and achieving excellent efficacy. This review describes in detail the physiological structure and barriers of the lungs and the structure of liposomes; then summarizes the application of liposomes in different lung diseases, as well as its drawbacks and advantages. Finally, we suggest that liposome-delivered nucleic acids are expected to be a new trend and approach for the treatment of lung diseases.

Keywords: liposomes, delivery system, lung disease, Lung anatomy

Introduction

The lung is the core organ of the human respiratory system, and its main function is to realize efficient gas exchange between the body and the external environment.¹ The lungs are mainly composed of branched airways and billions of alveoli at the ends. Alveoli are the basic functional units of the lungs. Their core role lies in achieving efficient gas exchange, and they also have important structural maintenance and defense functions. More importantly, in addition to the core respiratory function, the lungs also undertake important non-respiratory functions, defending against inhaled pathogens and particulate matter through the mucociliary system and immune cells, and filtering tiny emboli in the blood.² To sum up, lungs are extremely important organs in the human body.

The lungs are in the thoracic cavity, above the diaphragm, on both sides of the mediastinum, and cover the heart. They are divided into the left lung. The structure of the lungs is precise and efficient. The internal branches form a complex bronchial tree network, with hundreds of millions of thin-walled alveoli connected at the ends, forming a huge gas exchange interface.³ Air enters the left and right main bronchi through the trachea and then branches step by step into the lobar bronchi, segmental bronchi, small bronchi, thin bronchi until the terminal thin bronchi, and finally flows into the respiratory thin bronchi, alveolar ducts and alveolar sacs. The alveoli are the basic units of gas exchange, composed of extremely thin type I alveolar epithelial cells and scattered type II alveolar epithelial cells. Their walls are closely attached to a dense network of capillaries, forming a huge surface area for gas exchange.

The barrier of the lungs is a sophisticated multi-level defense system, with the core objective of protecting the fragile interface of qi and blood exchange and maintaining the stability of the internal environment. As shown in Figure 1B-D, the pulmonary barrier system is primarily categorized into the following components: 1) Physical barriers; 2)

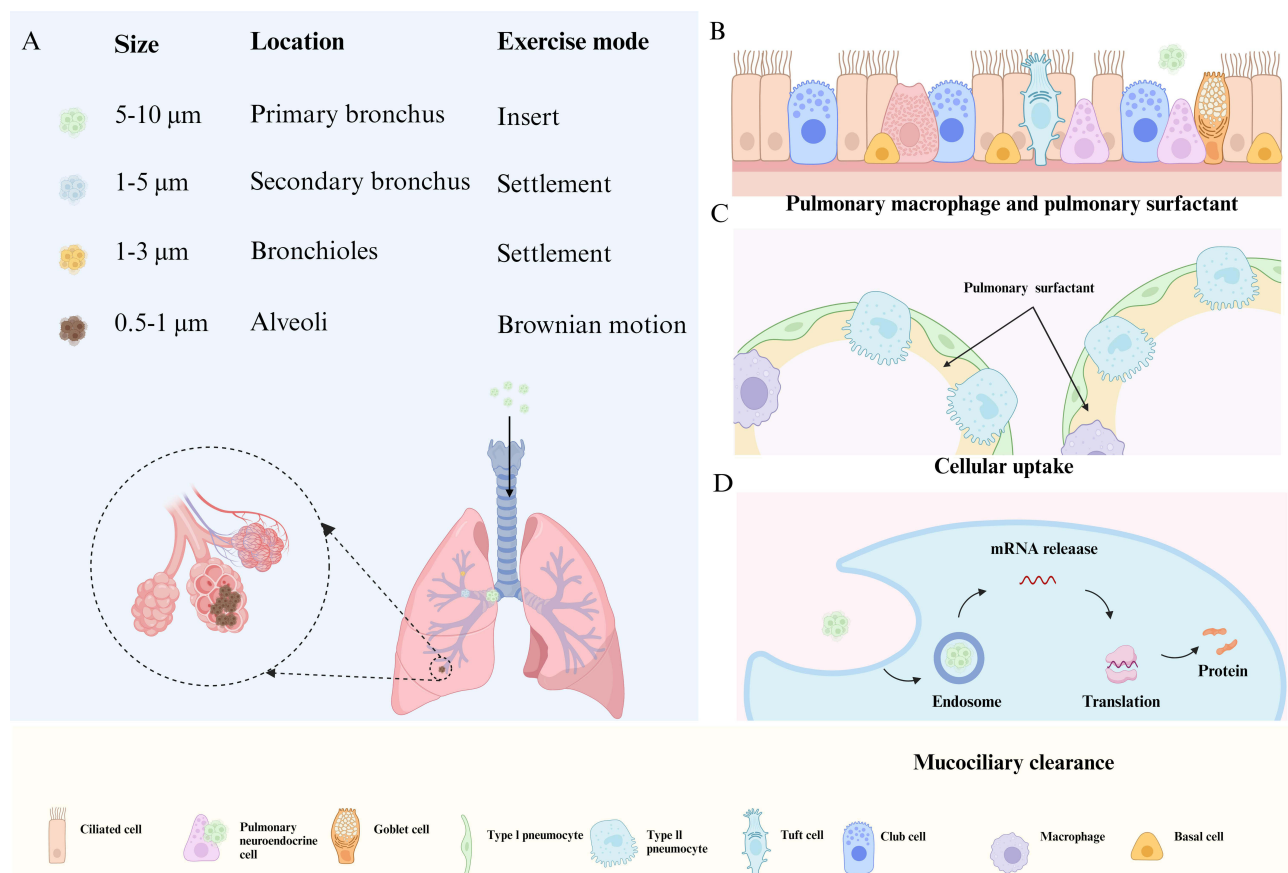


Figure 1 (A) Pulmonary inhalation of material processes and the deposition locations and movement patterns of substances with different particle sizes; (B) Mucus cilia removal; (C) Alveolar macrophages and lung surface-active substances play a scavenging role; (D) Cellular and intracellular barriers. Created in BioRender. Xi, Z. (2025) <https://BioRender.com/th2j0ee>.

Biochemical barriers; 3) Cellular immune defenses; 4) The blood-gas barrier; and 5) Immunomodulatory factors. Then we will make a simple summary of these barriers. The mechanism of the physical barrier mainly involves the secretion of mucus by goblet cells in the airway epithelium to adhere to particulate matter, and the directional movement of cilia to remove foreign substances.⁴ Meanwhile, a closed barrier is formed between airway epithelial cells through tight junction proteins, preventing pathogens from penetrating. Finally, the foreign object stimulates the airway, triggering a strong exhaled airflow and physically expelling large particles. The biochemical barrier of the lungs mainly works by utilizing antibacterial substances, such as lysozyme, lactoferrin and defensins, etc.⁵ These antibacterial substances are directly used to kill pathogens, inhibit microbial colonization, regulate immune responses and maintain tissue homeostasis, thus forming a multi-level innate immune defense system. The cellular immune barrier of the lungs is collaboratively maintained by alveolar macrophages that continuously monitor and eliminate pathogens, dendritic cells that initiate adaptive immune responses, neutrophils that rapidly kill microorganisms, and NK cells that precisely target infected cells.⁶ Together, they form an intricate defense network safeguarding lung tissue homeostasis. The blood-gas barrier of the lungs is composed of an ultrathin structure of alveolar epithelial cells, basement membranes and capillary endothelial cells, which separates the alveolar cavity from the blood flow, allowing for efficient exchange of oxygen and carbon dioxide while preventing the transmembrane diffusion of pathogens and macromolecular substances.⁷ The immune regulatory barrier of the lungs maintains immune homeostasis by suppressing excessive inflammation through regulatory T cells, balancing immune responses with anti-inflammatory factors (such as IL-10), and transforming the phenotype of alveolar macrophages, achieving a dynamic balance between defense and tolerance.⁸ Damage to the lung barrier will trigger a vicious cycle: the failure of physical clearance leads to the retention of pathogens and particulate matter, inducing chronic inflammation (such as bronchitis); The disruption of the blood-gas barrier enables bacteria/liquids to

invade the alveoli, causing pneumonia, pulmonary edema and even respiratory failure. Long-term damage can lead to irreversible lung tissue lesions (such as pulmonary fibrosis and chronic obstructive pulmonary disease), eventually resulting in progressive loss of respiratory function.

In recent years, compared with systemic drug administration, research on the use of different delivery systems to deliver drugs to the lungs for the treatment of lung diseases has attracted increasing attention from researchers. The main advantages of drug delivery through the lungs are as follows. First, since the metabolic rate of drugs in the lungs is much lower than that in the liver. Therefore, lung delivery of drugs can avoid the first-pass effect, thereby greatly improving the bioavailability of drugs in vivo. Then, delivering drugs through the lungs can avoid the influence of acidic pH in the gastrointestinal tract, intestinal microorganisms and special enzymes on certain drugs, and will not cause unknown reactions with food in the digestive tract. Therefore, delivering therapeutic drugs through the lungs is a highly promising treatment approach.

Although lung delivery has many advantages. However, there are certain limitations in drug delivery to the lungs, although the direct delivery of drugs to the lungs is limited. The defense mechanism of the respiratory tract can prevent the entry of foreign substances, thus posing certain obstacles to the direct delivery of drugs to the lungs. Then, lung delivery of drugs has relatively strict requirements for the size of the drugs or particles. Therefore, how to ensure that the drug can be accurately delivered to the lesion site. This requires considering the aerodynamics of the particles and their size. Then, we summarized the aerodynamics and deposition sites of particles of different sizes. As shown in [Figure 1A](#), the deposition of inhaled particles in the airways is influenced by multiple mechanisms. Among them, the aerodynamic diameter (AD) of the particles largely determines the deposition mode of the particles.^{9–11} It mainly falls into the following situations: 1) Larger particles with AD more than 5 μm may be impacted in the upper airway and atmospheric airway.¹² This usually leads to the deposition of particles in the oropharynx area, increasing the risk of them entering the gastrointestinal tract rather than the airways. 2) AD particles between 1 and 5 μm will undergo gravitational sedimentation and deposit in the lower airway, terminal bronchioles and alveoli. 3) Nanoscale particles with AD below 1 μm can penetrate deep into the alveoli and randomly diffuse through Brownian motion. Ultrafine particles with AD below 1 μm can not only diffuse into the alveolar area but also into the trachea and bronchi area, which promotes the wide distribution of drugs encapsulated by the delivery system throughout the lungs. However, different respiratory diseases affect different locations of the lungs. For instance, asthma mainly affects the upper airway, while COPD mainly affects the distal alveoli.¹³ Therefore, to successfully deliver drugs to the desired location, particle size is one of the important parameters that determine whether the delivery system can bypass physiological barriers and clearance mechanisms.

Nowadays, an increasing number of researchers are utilizing various drug delivery systems, such as liposomes, hydrogels, and biological carriers, which can address the issues associated with traditional treatment methods. Among them, nano delivery systems are widely used in drug delivery, cancer treatment, and other fields due to their excellent biocompatibility. We compared liposomes, solid lipid nanoparticles, polymer nanoparticles, and extracellular vesicles ([Table 1](#)). Detailed comparisons were made in terms of materials, structure, and drug loading types. Comparison shows that due to the unique structure and good drug loading rate of liposomes, they have been widely used in drug delivery systems, and some liposomes have already been launched on the market. Liposomes are also a prominent delivery system in nano delivery systems. Liposomes were proposed in 1964, with a diameter between 100–500 nm, mainly composed of self-assembled phospholipids.¹⁴ Phospholipids are composed of polar phosphate head groups and hydrophobic lipid tails.¹⁵ With the continuous deepening of research, human interest in liposome delivery drug therapy for diseases is increasing. Recently, due to the official approval of liposomes by the US FDA as a therapeutic carrier for drug delivery, liposomes have continuously entered clinical trials and achieved excellent therapeutic effects ([Table 2](#)). Liposomes self-assemble into a unique structure with a lipid membrane and a hydrophilic core, like the structure of cell membranes. As shown in [Figure 2](#), liposome can be used to deliver hydrophobic and hydrophilic molecules and have biocompatibility and biodegradability. Liposomes possess characteristics such as enhancing the solubility of encapsulated substances, reducing the adverse reactions and toxicity of free drugs, flexible charge and size regulation, and the ability to undergo surface modification.^{16,17} Liposomes can deliver drugs to the lesion site through passive targeting. When inflammation or infection occurs at the lesion site, the endothelial space of the blood vessels will widen, which may cause liposomes to remain at the lesion site and thus achieve therapeutic effects.¹⁸ More importantly, unmodified liposomes may be captured

Table 1 Comparison of Different Nano Delivery Systems

Carrier	Material	Structure	Type of Drug Loaded	Drug Loading Rate	Preparation Process	Listed Drugs	Ref.
Liposomes	Natural phospholipids, cholesterol, and synthetic phospholipids.	Phospholipid bilayer enveloping aqueous core	Hydrophilic drugs, hydrophobic drugs	Medium	Mature	Arikayce [®] (Amikacin Liposomes)	[20]
Solid lipid nanoparticles	Glycerol tristearate, glycerol monostearate, and polysorbate 80.	A core composed of solid lipids, surrounded by a stable outer shell formed by surfactants	Hydrophobic drugs, amphiphilic drugs	Medium	Mature	None	[21]
Polymeric nanoparticle	Chitosan and PLGA, etc	Polymer matrix encapsulating drugs	Broad-spectrum	Medium	Mature	None	[22]
Exosomes	Mesenchymal stem cells, etc	Phospholipid bilayer vesicles secreted by natural cells	Small molecules, nucleic acids, proteins	Low	Complex	None	[23]

Table 2 Liposomal Delivery of Drugs for the Treatment of Clinical Diseases

Clinical Trial Number	Research Start Time	Test Name	Disease Name	Condition	Stage	Ref
NCT00250068	2003-04	Study of Aerosolized Liposomal 9-Nitro-20 (S)-Camptothecin (L9NC)	Pulmonary malignancies	Study Completion	Phase 2	[24]
NCT00059605	2003-03	Phase I Study of IV DOTAP: Cholesterol-Fus1 in Non-Small-Cell Lung Cancer	Lung cancer	Study Completion	Phase 1	[25]
NCT04381910	2020-09	Irinotecan Hydrochloride Liposome Injection (LY01610) For Small Cell Lung Cancer	Lung cancer	Study Completion	Phase 2	[26]
NCT03088813	2018-04	Study of Irinotecan Liposome Injection (ONIVYDE®) in Patients with Small Cell Lung Cancer (RESILIENT)	Small Cell Lung Cancer	Study Completion	Phase 3	[27]
NCT01315236	2012-04	Liposomal Amikacin for Inhalation (LAI) for Nontuberculous Mycobacteria	Nontuberculous Mycobacterial Lung Disease	Study Completion	Phase 2	[28]
NCT02996214	2016-11	Paclitaxel Liposome for Squamous Non-Small-cell Lung Cancer Study (LIPUSU)	Lung squamous cell carcinoma	Study Completion	Phase 4	[29]
NCT03038178	2016-10	Liposomal Amikacin for Inhalation (LAI) in the Treatment of Mycobacterium Abscessus Lung Disease	Mycobacterium abscessus lung disease	Study Completion	Phase 2	[30]
NCT02273661	2014-11	Evaluation of a Therapeutic Strategy Including Nebulised Liposomal Amphotericin B (Ambisome®) in Maintenance Treatment of Allergic Bronchopulmonary Aspergillosis (Cystic Fibrosis Excluded)	Allergic bronchopulmonary aspergillosis	Study Completion	Phase 2	[31]
NCT01515007	2014-03	Phase 3 Study with Ciprofloxacin Dispersion for Inhalation in Non-CF Bronchiectasis (ORBIT-3)	Non-cystic fibrosis bronchiectasis	Study Completion	Phase 3	[32]
NCT01316276	2012-10	Extension Study of Liposomal Amikacin for Inhalation in Cystic Fibrosis (CF) Patients with Chronic <i>Pseudomonas Aeruginosa</i> (Pa) Infection	Cystic fibrosis with chronic <i>P. aeruginosa</i> infection	Study Completion	Phase 3	[33]
NCT00777296	2007-02	Multidose Safety and Tolerability Study of Dose Escalation of Liposomal Amikacin for Inhalation (ARIKACE™)	<i>Pseudomonas aeruginosa</i> infection	Study Completion	Phase 2	[34]
NCT01334892	2009-12	L-CsA in the Prevention of Bronchiolitis Obliterans Syndrome (BOS) in Lung Transplant (LT) Patients	Bronchiolitis Obliterans Syndrome	Study Completion	Phase 3	[35]
NCT01315678	2012-02	Study to Evaluate Arikayce™ in CF Patients with Chronic <i>Pseudomonas Aeruginosa</i> Infections	Chronic <i>Pseudomonas aeruginosa</i> infection	Study Completion	Phase 3	[36]
NCT04378920	2020-04	A Study of Liposomal Trans Crocetin, LEAF-4L6715, in Patients with Acute Respiratory Distress Syndrome Due to COVID-19, Sepsis or Other Causes	COVID-19-related ARDS	Study Completion	Phase 2	[37]
NCT02583373	2016-03	Safety, Tolerability, Efficacy and Pharmacodynamics of CAL02 in Severe Pneumonia Caused by Streptococcus Pneumoniae	Pneumococcal pneumonia	Study Completion	Phase 1	[38]

by the mononuclear macrophage system and actively accumulate in organs such as the liver and spleen. Meanwhile, since the surface of liposomes is easy to modify, precise delivery can be achieved by modifying specific carriers on the surface.¹⁹ Antibodies, polypeptides and sugar chains can be modified on the surface, enabling liposomes to actively recognize and bind to target cells, and then release drugs to achieve therapeutic purposes. At present, due to the unique physical properties and good biocompatibility of liposomes, researchers use liposomes to encapsulate drugs for the treatment of clinical diseases. Excitingly, some liposomes have been successfully marketed and achieved good therapeutic effects. We have summarized the currently marketed liposomes (Table 1).

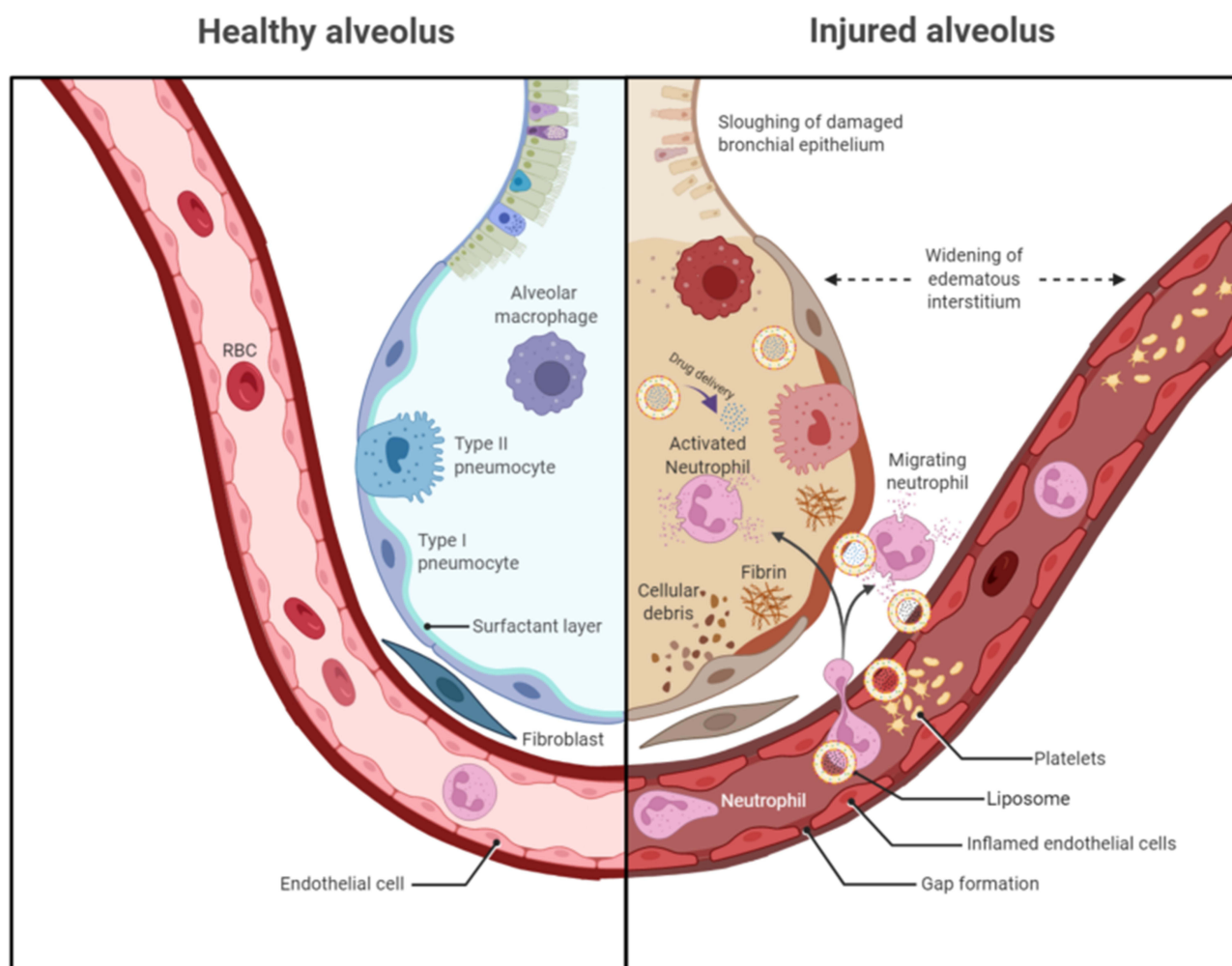


Figure 2 Liposomes release drug at diseased alveoli through blood circulation. Created in BioRender. Xi, Z. (2025) <https://BioRender.com/zrpched>.

This study focuses on summarizing the structure, pharmacokinetics and liposomes that have entered clinical applications (Table 2). It also provides a detailed insight into the current applications of liposomes in different lung diseases, such as pneumonia, COPD, idiopathic pulmonary fibrosis and lung cancer. We have analyzed the advantages and disadvantages of these therapeutic approaches. More importantly, we conclude with an outlook on liposome-delivered gene therapy and an analysis of the disadvantages that currently exist.

Liposome

Liposomes are nanoscale spherical vesicles composed of phospholipid bilayers that mimic the structure of natural cell membranes, exhibiting excellent biocompatibility and biodegradability. These vesicular carriers enhance therapeutic efficacy by stabilizing the chemical properties of therapeutic agents, overcoming cellular and tissue uptake barriers, and improving biodistribution to target sites *in vivo*. This targeted delivery mechanism significantly minimizes systemic drug toxicity while optimizing therapeutic outcomes.³⁹ As drug delivery systems, liposomes possess the unique capability to co-encapsulate both hydrophilic and hydrophobic therapeutics. Through surface engineering with targeting moieties such as antibodies, proteins, or ligand-receptor complexes, these nanostructured carriers can either prolong systemic circulation duration or achieve site-specific delivery to designated cellular and tissue targets, demonstrating enhanced therapeutic precision through spatial control of drug release.^{14,40} Nowadays, liposomes are widely used in anti-tumor drugs, gene delivery and vaccine delivery, etc.⁴¹ In this section, the structure of liposomes is introduced first, and the pharmacokinetic characteristics are described in detail.

Secondly, summarize in detail the current market applications and potential of liposomes. Finally, the clinical problems existing in liposomes were analyzed to provide corresponding insights.

Liposome Structure and Classification

The main component of liposomes is glycerophospholipids, which are amphiphilic lipids composed of glycerol molecules bound to a phosphate group and two saturated or unsaturated fatty acid chains (Figure 3A). Liposome membranes can be composed of one or more lipid bilayer layers surrounding the internal water nucleation tissue, with polar head bases facing the internal and external water phases.⁴² This special structure provides liposomes with the ability to load and deliver molecules of different solubilities. Hydrophilic molecules are in the inner water nucleus, hydrophobic molecules in the lipid bilayer, and amphiphilic molecules at the interface of the water/lipid bilayer. The core components of liposomes are mainly phospholipids and cholesterol. Phospholipids are one of the important skeletons of liposomes. Common phospholipid molecules mainly include natural phospholipids and synthetic phospholipids. The proportion of cholesterol is usually 30–50%. It reduces the fluidity of the membrane by filling the gaps in the phospholipid tails, thereby reducing drug leakage and ultimately ensuring that the drug can be better encapsulated within the liposomes.⁴³ As shown in Figure 3B, liposomes can be classified into three types: 1) monolayer liposomes: mainly used for targeted drug delivery; 2) Multilayer liposomes: Containing multiple concentric phospholipid layers (with a layer spacing of approximately 4–6 nm), they are suitable for sustained-release macromolecule drugs; 3) Polycystic liposomes: Non-concentric multi-lumen structure, drug loading capacity can reach over 30%, suitable for the delivery of large quantities of drugs.⁴⁴ Due to the easy modification of the surface of liposomes, we can modify different antibodies, proteins and targeted peptides on their surfaces according to different usage scenarios to precisely deliver drugs (Figure 3C). The surface of liposomes is modified with monoclonal antibodies or their fragments targeting EGFR or TfR, and at the same time, anti-tumor drugs are loaded. Through receptor-mediated endocytosis, the drugs are efficiently delivered into the interior of cancer cells, enhancing the anti-cancer effect and reducing damage to normal lung tissue.⁴⁵

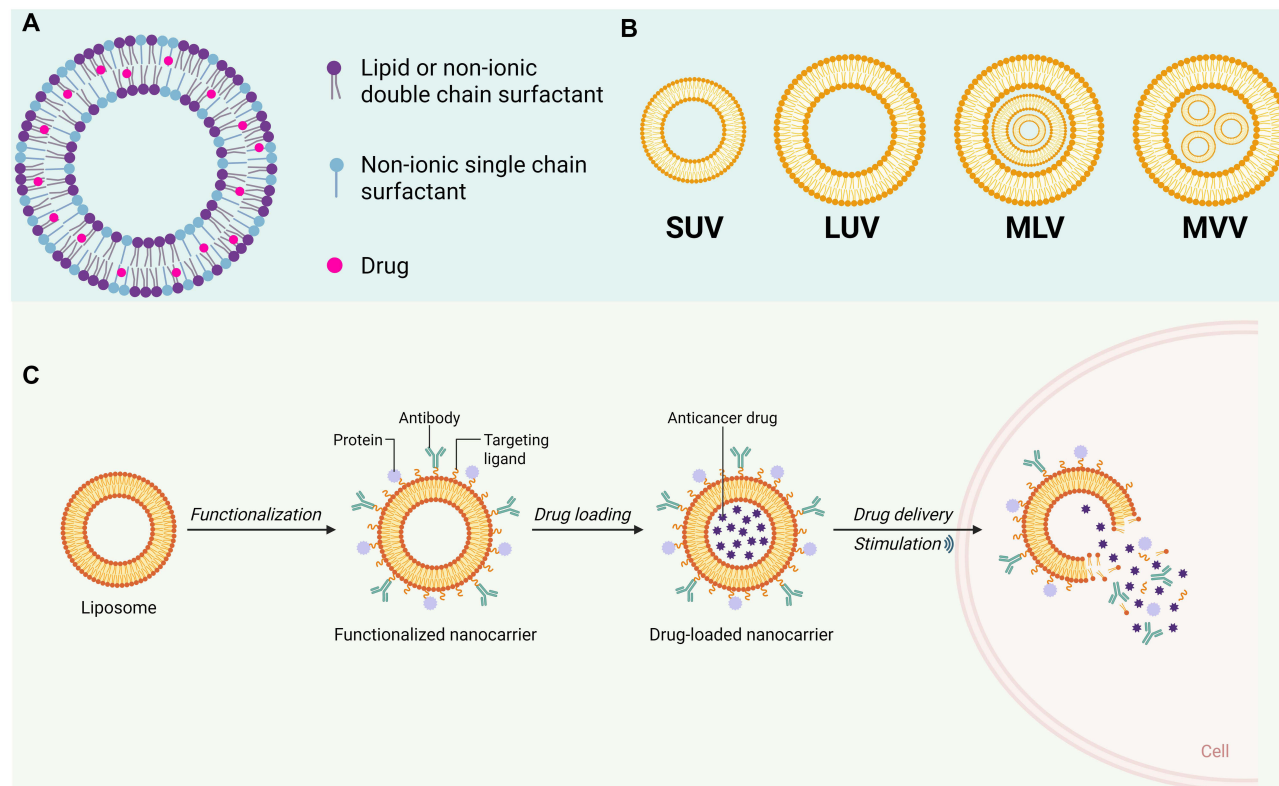


Figure 3 (A) The structure of liposomes; (B) Classification of liposomes (C) Liposome drug delivery. Created in BioRender. Xi, Z. (2025) <https://BioRender.com/131uux8>.

At the same time, it is also possible to modify the surface with antibodies that can specifically recognize pathogen surface antigens, aptamers that can bind with high affinity to bacterial surface components, or peptide ligands that can simulate the host receptor binding domain. This type of liposome can actively target and precisely deliver antibiotics to the infection site and the area around the pathogen, significantly increasing the local drug concentration, effectively penetrating the biological membrane, and overcoming the problems of insufficient local concentration and high systemic toxicity in traditional drug administration methods. In conclusion, in the future, different liposomes can be designed based on their specific structures for the delivery of various drugs, ultimately achieving more precise drug delivery goals.

General Pharmacokinetic Characteristics of Liposomes

Liposomes mainly enter the cell through endocytosis to release drugs. Liposomes have a series of pharmacokinetic advantages, such as specific drug delivery, high metabolic stability, high membrane permeability and improved drug bioavailability, etc. Different administration methods of liposomes and different particle sizes, charges and targeting properties will all affect the pharmacokinetic behavior of liposomes. The size of liposome particle size is one of the key factors determining whether it can effectively perform biological functions in vivo. The latest research indicates that liposomes with a particle size of less than 200 nm are more likely to pass through the vascular endothelial space or follicular epithelial cells (such as M cell), prolonging the circulation time and enhancing tissue penetration, thereby increasing the accumulation of drugs at the target site.⁴⁶ Liposomes with a particle size more than 500 nm are more easily recognized and rapidly cleared by the reticuloendothelial system, leading to a rapid decrease in blood drug concentration. Therefore, when designing liposomes, the size of the liposomes should be carefully considered to ensure that they can have better therapeutic effects. In practical work, it is usually necessary to design a delivery system suitable for the characteristics of the disease based on the properties of liposomes. For example: In patients with IPF, since the treatment requires a certain blood drug concentration, liposome nanoparticles with larger particle size and faster excretion cannot be used for the treatment of IPF. Liposomes are mainly administered orally or by injection. The main administration methods of liposomes are as follows: 1) Intravenous injection; 2) Oral administration; 3) Inhalation administration.^{47,48} Different administration methods have different pharmacokinetic characteristics. Liposomes can directly enter the bloodstream through intravenous injection (Table 3). By regulating their particle size between 100 and 200 nm, they can reduce the rapid clearance of the endothelial system to maintain the required blood drug concentration throughout the body.⁴⁹ The core purpose of inhalation administration is to prolong the retention time of drugs in the alveoli and interstitial lung tissue. Usually, liposomes of 5–10 μ m are selected to achieve alveolar deposition. However, inhalation administration needs to overcome the dual barriers of mucociliary clearance and macrophage phagocytosis.⁵⁰ Therefore, researchers considered modifying its surface to enable liposomes to avoid being cleared by liquid cilia and phagocytosed by macrophages. Although oral administration is the most convenient way of drug administration, it is highly challenging. The main reason might be that oral administration will encounter gastrointestinal enzymatic hydrolysis and mucosal absorption disorders. To sum up, in practical applications, the corresponding drug administration methods should be designed based on the characteristics of different lung diseases. However, due to the special barrier system of the lungs and the phagocytosis of macrophages, it is difficult for liposome to maintain the required blood drug concentration in the lungs.^{51,52} Therefore, how to solve the problem of the residence time of the nano-delivery system in the lungs will become a major challenge.

Clinical Potential of Liposomes

The composition of liposomes is very similar to that of the biological membranes of mammals. Most liposomes have excellent biocompatibility and biodegradability. Liposomes, as the first delivery system approved by the US FDA for the treatment of diseases, have been widely used in the treatment of various diseases and achieved excellent results. More importantly, liposome delivery drugs have already been marketed as finished drugs at present. In 1995, the FDA of the United States approved Doxil (liposome doxorubicin) for the treatment of cancer.⁶⁰ Doxil is an adriamycin-specific agent encapsulated in a monolayer of liposomes covered with PEG called “polyethylene glycol liposomes”, which allow for precise delivery of the drug around the tumor cells through passive targeting. One of the biggest advantages of Doxil is that it significantly reduces the side effects of the medication, especially for the heart and the skin.⁶¹ Nowadays, more and

Table 3 Different Types of Nano Inhalation Method

Type	Size	Load Drugs	Administration Method	Animal Model	Preclinical Trial Results	Ref.
Liposome Liposome	116 nm	Agastache flavonol	Nebulized inhalation	Mice	By exerting anti-inflammatory effects and repairing the lung barrier, it significantly improves the acute lung injury phenotype and inhibits the activation of the TLR4-NF- κ B/MAPK pathway, which is the pathological mechanism of acute lung injury.	[53]
Liposome	150 nm	mRNA	Nebulized inhalation	Mice	The therapeutic potential of NF-LNPs in neonatal bronchopulmonary dysplasia (BPD) and adult idiopathic pulmonary fibrosis (IPF) models were further demonstrated by delivering the mRNA encoding group D member 1 of the nuclear receptor subfamily 1 (NR1D1).	[54]
Liposome	100 nm	Dihydroartemisinin and Calcium phosphate	Nebulized inhalation	Mice	The enhanced ferroptosis process centered on Ca ²⁺ stress-induced ER stress is a process of cell swelling and cell membrane damage driven by significant intracellular ROS and LPO accumulation. The proposed liposome has shown lung retention characteristics and extraordinary anti-tumor ability in the upright lung tumor mouse model.	[55]
Polymer nanoparticles PLGA	42 nm	Indocyanine green	Nebulized inhalation	Mice	Effective delivery and treatment of deep lung infections have been achieved, significantly reducing the bacterial load on the lungs of infected mice, while alleviating inflammation and damage, demonstrating a promising clinical application prospect	[56]
PLGA nano	100 nm	Nintedanib and Pirfenidone	Nebulized inhalation	Mice	It can reduce the progression of fibrosis, restore the physiological function of the lungs, inactivate myofibroblasts, inhibit the progression of TGF- β , suppress the production of ECM components (collagen I and α -SMA), and prolong the retention time of the lungs.	[57]
Exosomes Mesenchymal stem cells	168 nm	None	Nebulized inhalation	Mice	Exosomes inhibit STAT3 phosphorylation through the STAT3/Krt8/AQP5 axis, promoting the transdifferentiation of transitional cells into AECIs and accelerating the regeneration of alveolar epithelium after LPS-induced lung injury.	[58]
Stem cells	50 to 400 nm	None	Nebulized inhalation	Human	The patients who received EVs treatment showed significant improvement in their lung function, with both forced vital capacity (FVC) and maximal voluntary ventilation (MVV) significantly increased. Moreover, the patients' perceived quality of life also improved significantly, and symptoms such as coughing and breathing difficulties were significantly alleviated.	[59]

more liposome-loaded therapeutic drug products are being marketed due to the excellent biosafety and powerful delivery capabilities of liposomes. Doxorubicin hydrochloride liposome, the world's first anti-cancer liposome formulation, has sales of more than 5 billion yuan in China by 2021.⁶² Meanwhile, liposomes loaded with amphotericin have been touted as the “last straw” for patients with invasive fungal infections, with a 20-fold increase in hepatic targeting and a 75% reduction in nephrotoxicity compared to conventional reagents.^{63,64} Liposomes can deliver not only small molecule drugs, but also mRNA and nucleic acid-based drugs. In 2020, Hong et al⁶⁵ first used liposomal delivery of miR-34a to treat patients with advanced solid tumors. Although the experiment was prematurely ended due to the death of the patient, it can still be proved that liposomes are feasible for the delivery of nucleic acid drugs to treat diseases. In summary, liposomes have become a mature drug delivery system for disease treatment with a wide range of future market applications.

Inhalation Administration

Inhalation preparations refer to the process where drugs are made into aerosols through special drug delivery devices and are directly deposited in the respiratory tract and lungs by patients through active or passive inhalation.⁶⁶ Due to the unique physiological structure of the lungs, inhalation preparations can deliver drugs to the lesion site, greatly reducing the side effects of the drugs.⁴⁸ At the same time, compared with administration methods such as injection, inhalation preparations are more easily accepted by patients. This might be because inhalation administration is a painless operation. We have summarized a table to summarize liposomes, polymer nanoparticles and exosomes. The summaries were made respectively in terms of size, particle size, administration method, animal model and preclinical effect. With the development of science and technology, inhalation drug delivery has become one of the directions that researchers are interested in (Table 4). With the development of science and technology, inhalation drug delivery has become one of the directions that researchers are interested in.⁶⁷ 1) Systemic side effects have been significantly reduced. The dosage of the drug is low, and it mainly takes effect locally, with a small amount of the drug entering the bloodstream.⁶⁸ 2) High local drug concentration enhances therapeutic effect. The drug reaches a high concentration in the target organ, while the concentration in other parts of the body is relatively low.⁶⁹ 3) It takes effect rapidly. The drug directly acts on the smooth muscles, mucous membranes or inflammatory cells of the airways without going through the systemic blood circulation.⁷⁰ In conclusion, inhalation administration is a highly promising drug delivery method. When combined with liposome therapy for lung diseases, it may achieve better therapeutic effects.

Table 4 Clinically Marketed Products for Liposomal Therapy of Diseases

Product Name	Indication	Listed Company	Healing Effect	Ref.
Arikayce [®]	Non-tuberculous mycobacterial lung disease (MAC)	Insmed	Sputum culture conversion rate 29%	[71]
AmBisome [®]	Fungal infections of the lungs	Gilead Sciences	Fungal clearance 84%	[72]
Lipusu [®]	Non-small cell carcinoma	Nanjing Sike Medicine Industry Co., Ltd.	Extending the life span of patients with advanced NSCLC	[73]
Pulmaquin [®]	Cystic fibrosis in <i>Pseudomonas aeruginosa</i> infection	Aradigm	Reduced frequency of administration and systemic toxicity	[74]
LipoBiEDT-TOB	<i>Pseudomonas aeruginosa</i> lung infection	Halwani et al	Reduced production of group-sensing molecules and virulence factors	[75,76]
Doxil [®]	Non-small cell carcinoma	Janssen Biotech, Inc.	Significantly reduced cell proliferation in vitro and improved survival in vivo in NSCLC patients	[77]
Onivyde [®]	Second-line treatment of metastatic pancreatic cancer	Ipsen	Prolonged overall and progression-free survival	[78]

Liposome Delivery Systems in Lung Disease

Liposomal delivery systems have achieved good therapeutic results in some diseases. However, due to the special barrier effect of the lungs, how to deliver drugs to the lesion site accurately becomes a major challenge. The physiologic barrier of the lungs not only clears inhaled medications as foreign bodies by the regular oscillation of cilia, but also macrophages phagocytose the therapeutic drug and then expel it from the body, both of which prevent the drug from reaching the lungs for therapeutic purposes. At the same time, the diameter and stability of the delivery system indirectly affects whether the drug can be accurately delivered to the lesion. When the diameter of the delivery system is greater than 5 μm , the delivery system tends to get stuck in the throat and cannot finalize the delivery. When the delivery system is less than 1 μm , it is easy to be exhaled out of the body and difficult to be accumulated in the body.⁷⁹ These challenges then contribute to the difficulty of administering liposomal drug delivery systems in the lungs, as well as the difficulty of maintaining the body's desired blood levels. In this section, we not only summarize the therapeutic role and delivery mechanism of liposomal delivered drugs in different lung diseases, but also the advantages and current problems of liposomes.

Pneumonia

Pneumonia is one of the leading causes of patient death in the world.⁸⁰ Pneumonia is an inflammation of the lungs triggered by pathogens such as bacterial, viral, and fungal infections, or by non-infectious factors such as inhalation of foreign bodies and noxious gases, mainly involving the alveoli and interstitium of the lungs. Patients often present with fever, cough, chest pain and dyspnea, and in severe cases may be accompanied by confusion or cyanosis of the skin.⁸¹ The traditional means of treating pneumonia are usually oral, nebulized inhalation or intravenous administration of appropriate therapeutic drugs. Due to the unique circulatory system of the lungs, large drug concentrations are often required to maintain the blood levels needed for treatment, and large doses can bring about a range of complications and unavoidable damage to the patient's organism. Liposome delivered drugs can maintain the patient's desired blood levels by passively or actively targeting the lesion site.

Bacterial Pneumonia

Bacterial pneumonia is mainly categorized into community-acquired pneumonia and hospital-acquired pneumonia, both caused by bacterial infections. The latest surveys show that no less than 2.4 million people of all ages die from lower respiratory infections caused by bacteria.⁸² Among them, the mortality rates are higher in Africa, Southeast Asia and South Asia.⁸² However, antibiotics remain a cornerstone in the treatment of bacterial pneumonia, the emergence of bacterial resistance and the potential for drug-induced toxicity pose significant clinical challenges. Liposome-mediated antibiotic delivery has emerged as a promising strategy to enhance therapeutic efficacy while mitigating these limitations. *Staphylococcus aureus* (*S. aureus*) is a common pathogen causing pneumonia with a high mortality rate.⁸³ Integrin $\alpha 5\beta 1$ plays a key role in *S. aureus* invasion of nonphagocytic cells and promotes the development of *Staphylococcus aureus* pneumonia. The delivered siRNA is designed to specifically target the $\alpha 5$ and $\beta 1$ subunits of integrin $\alpha 5\beta 1$, which is a key receptor for *Staphylococcus aureus* to invade respiratory epithelial cells and is only highly expressed on the surface of respiratory system-related cells such as the lungs, enabling siRNA to precisely silence the target protein.⁸⁴ Based on this, Meng et al⁸⁵ designed a liposome encapsulated siRNA to treat *Staphylococcus aureus* pneumonia caused by *S. aureus* through nebulization inhalation (Figure 4A). The experimental results demonstrated that endotracheal nebulization of siRNA-encapsulated liposomal drugs not only markedly alleviated the severity of *S. aureus* induced pneumonia (eg, reduction in bacterial load and enhancement of the immune response), but also effectively confined the infection to the pulmonary compartment, thereby preventing systemic dissemination (Figure 4C–E). It mainly adopts endotracheal nebulization for drug administration, which can directly deliver lipid nanoparticles (LNPs) encapsulated with siRNA to the lungs, avoiding drug loss caused by systemic distribution, significantly increasing local drug concentration in the lungs, and achieving targeted delivery to lung infection foci. Zhang et al⁸⁶ developed a liposome nanoparticle capable of targeting the lungs. It was shown by in vivo studies that liposomal nanoparticles effectively delivered siRNA to the lungs, resulting in a significant downregulation of target mRNA and TNF- α expression levels. Furthermore, this targeted delivery system markedly ameliorated pathological hallmarks of pulmonary inflammation. The

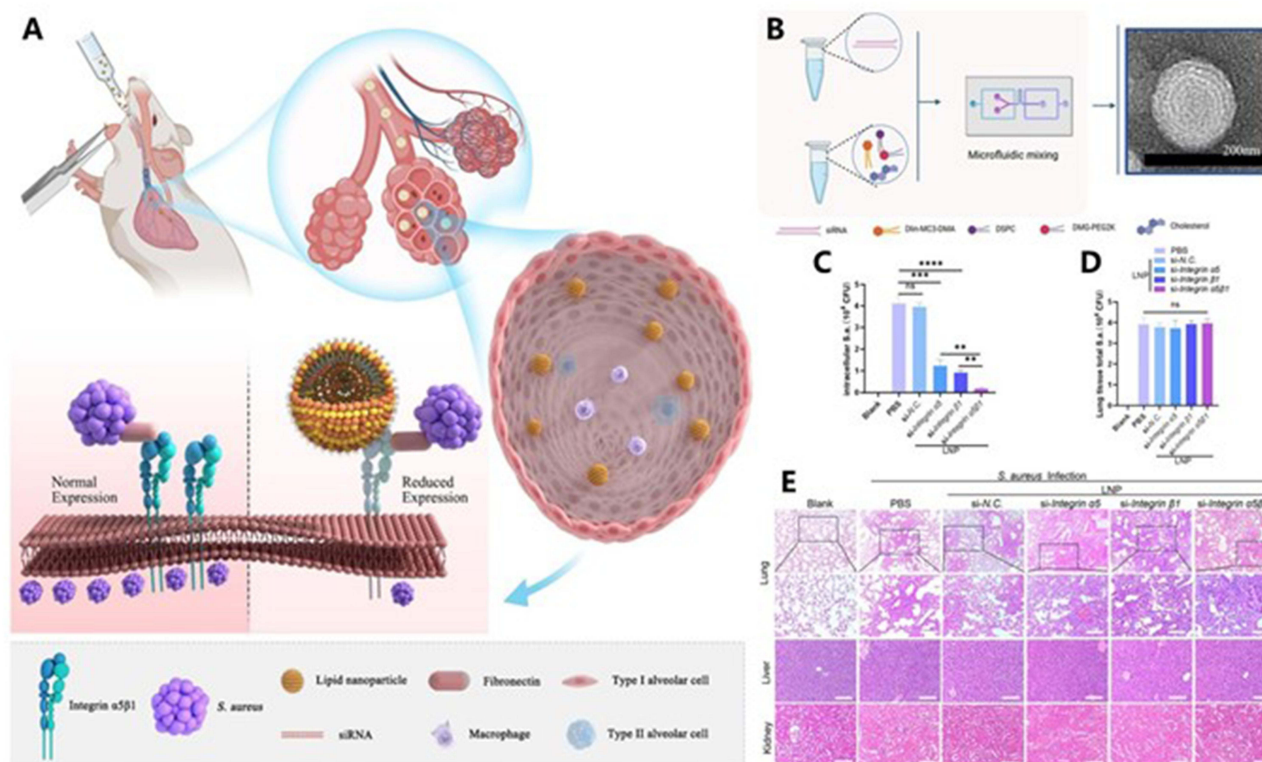


Figure 4 (A) Project diagram; (B) Characterization of LNPs before and after nebulization. LNP preparation. (C and D) Experimental animals were infected with *S. aureus* with the nebulization equipment (2×10^8 CFU) for 24 h. Total number of intrapulmonary bacteria. (E) Histological examinations of the main organs (lung, liver, and kidney). ns, $P > 0.05$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$. Modified with permission.⁸⁵ Copyright 2024, BMC.

liposome nanoparticles provide a novel therapeutic tool and method for the treatment of pneumonia. Liposomal drug delivery represents a highly promising yet imperfect therapeutic strategy for pneumonia treatment. While current studies have primarily evaluated in vitro safety profiles, comprehensive in vivo assessments remain limited. To fully establish the clinical potential of this approach, future research should systematically investigate critical pharmacokinetic parameters, including drug release kinetics and plasma concentration profiles to ensure the effectiveness and safety of the therapeutic measures. Traditional liposomes are usually composed of basic components such as phospholipids, cholesterol and polyethylene glycol (PEG).⁸⁷ However, traditional liposomes are often preferentially taken up and cleared by the mononuclear phagocyte system (MPS) in the body, especially Kupffer cells in the liver.⁸⁸ This tendency accumulation severely limits their application in the treatment of diseases related to extrahepatic tissues or organs. Therefore, Lee et al⁸⁶ developed a lung-targeted amphiphilic liposome that enhanced pulmonary enrichment of small interfering RNA (siRNA) drugs. In vitro and vivo studies showed that the liposome exhibited efficient cellular uptake, robust endosomal/lysosomal escape capabilities, and was able to significantly down-regulate the mRNA and protein levels of TNF- α and improve the pathological features of lung inflammation, which provided a novel strategy for achieving extrahepatic targeted delivery using liposomal systems.

Viral Pneumonia

COVID-19, respiratory syncytial virus, rhinovirus, human metapneumovirus, Zika virus, and influenza virus are the most common pathogens of viral pneumonia in both developed and developing countries.⁸⁹ The 2020 outbreak of New Crown infections killed tens of thousands of people, and in the early stages of treatment, high-dose shock therapy with drugs was necessary to slow the course of the disease,⁹⁰ however, this high-dose therapeutic regimen induces irreversible damage to healthy organs, potentially compromising long-term patient survival and quality of life. Macrophages are the key immune cells of the lungs and are the most important guardians of the respiratory system; they sense and phagocytose pathogens, release cytokines and participate in tissue repair.^{91,92} Zhao et al⁹³ reported that a liposomal nanoparticle (surface-

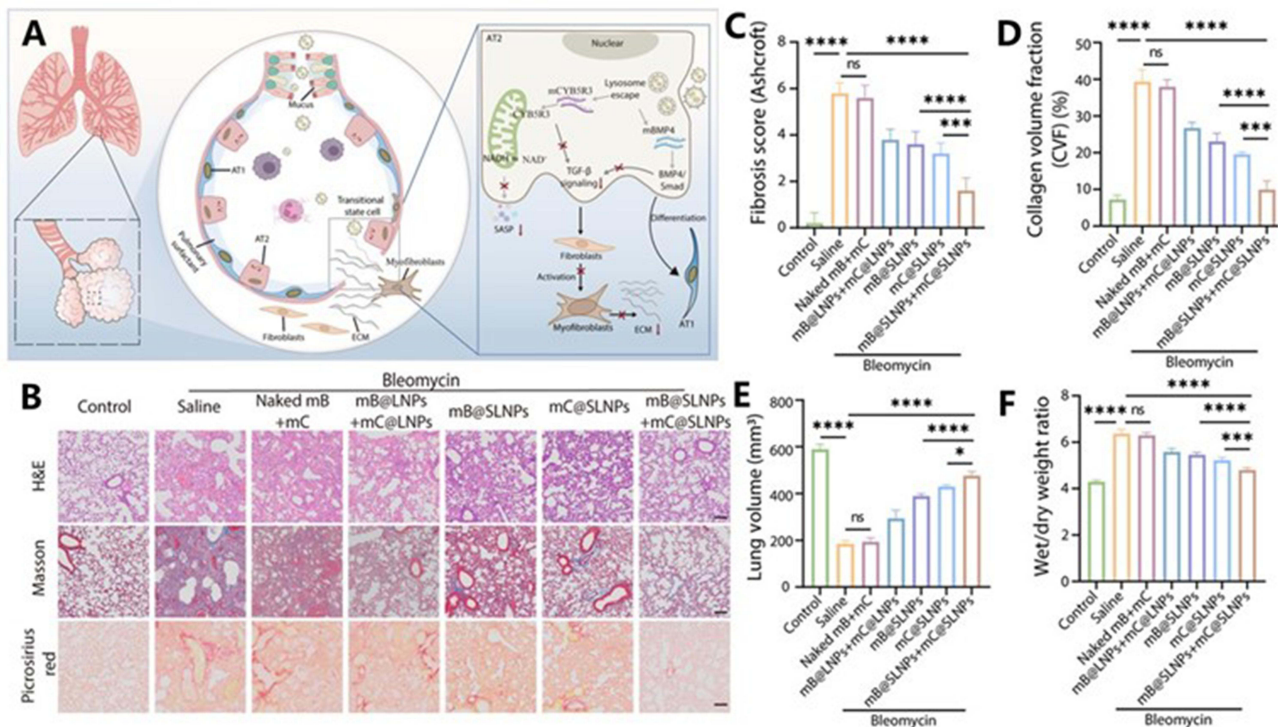
modified with macrophage-specific antibodies) can accurately deliver siRNA to macrophages. MacLNP was constructed by coupling the macrophage-specific antibody F4/80 to the surface of lipid nanoparticles (LNPs). F4/80 is a classic marker on the surface of mouse macrophages, which can specifically bind to macrophages, thereby precisely directing LNPs to macrophages. The experimental results demonstrated that siRNA delivery targeting TAK1 significantly reduced pro-inflammatory macrophage expression and ameliorated viral lung injury *in vitro* and *in vivo*. The structure of SARS-CoV-2 consists of four structural proteins: spiny protein (S), nucleocapsid (N), membrane (M), and envelope (E) proteins. E proteins are involved in virus assembly and maintenance of viral particles by binding to M proteins.⁹⁴ The latest research have shown that USP33-protein interaction removes K48-type polyubiquitin chains and enhances E-protein stability, thereby increasing its ability to induce cell death and inflammatory responses, and that knockdown of USP33 expression levels is beneficial in delaying disease progression. Zhou et al⁹⁵ utilized lipid nanoparticles to encapsulate siUSP33 and successfully delivered siUSP33 to mouse lungs. The experimental results showed that delivery of siRNA targeting USP33 to the lungs of mice using liposomes effectively attenuated the viral replication capacity and virulence in the mouse infection model. Liposome-delivered therapeutics for the treatment of viral pneumonia have achieved remarkable results, but more data supporting their safety and stability are needed to facilitate clinical translation. Tripterin/TP is a natural product with various biological activities, derived from the root bark of the traditional Chinese medicine Lei Gong Teng, which is one of the active ingredients in Lei Gong Teng Tablets and Lei Gong Teng Polyglycolide Tablets used in the treatment of rheumatoid diseases.⁹⁶ However, TP has disadvantages of low permeability, poor solubility, susceptibility to off targeting, and low oral utilization, factors that limit further clinical use of TP. Thus, Que et al⁹⁷ reported a TP-loaded liposome used to treat COVID-19. The liposome was prepared mainly by lipid membrane hydration extrusion method. The results of *in vitro* and *in vivo* experiments showed that this liposome has potent anti-inflammatory properties against severe COVID-19 hyperinflammation.

COPD

COPD is a heterogeneous lung disease characterized by chronic respiratory symptoms (dyspnea, cough, sputum and/or acute exacerbations) due to airway abnormalities (bronchiectasis, bronchiectasis minor) and/or alveolar abnormalities (emphysema) resulting in persistent, usually progressively worsening airflow limitation. The major environmental exposures to COPD are smoking, inhalation of toxic particles and gases from indoor and outdoor air pollution, and other environmental and host factors (including abnormal lung development and accelerated aging) may also contribute to the development of COPD.⁹⁸ COPD is an incurable disease that places a tremendous psychological and financial burden on the patient and the patient's family. The main treatment for COPD is still based on preventing infections, reducing inhalation of harmful particles, etc.⁹⁹ Quercetin holds significant promise as a candidate for COPD treatment due to its anti-inflammatory effects.¹⁰⁰ However, quercetin hinders further clinical applications due to poor water solubility and low bioavailability. Yin et al¹⁰¹ utilized liposomal encapsulation of quercetin to treat COPD. The results showed that the liposome significantly enhanced the ability to alleviate lung inflammation and anti-fibrosis by regulating the expression of inflammation-related factors and fibrosis signaling molecules. Berberine is an isoquinoline alkaloid that has shown therapeutic potential in COPD mice. A growing number of studies have focused on the effects of berberine on lung disease and have shown that berberine ameliorates cigarette smoke-induced airway inflammation in mice.¹⁰² However, the poor water solubility of berberine limits its clinical application. Liu et al¹⁰³ reported the study of a chitosanized liposome loaded with berberine for COPD treatment. The results showed that liposome could improve the inflammation score of lung tissues and reduce the levels of neutrophils and inflammatory cytokines (IL-1 β , IL-6, IL-17, and TNF- α) in alveolar lavage fluid, which provided a new idea and method for the treatment of COPD. Chinese medicine is a treasure of the Chinese nation, and more and more herbs can be developed for the treatment of COPD in the future. However, herbal medicines suffer from low biological activity and poor solubility. Liposomal delivery systems are well suited to address this difficulty. However, further careful evaluation of safety is still needed when utilizing liposomes to deliver herbal medicines.

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease of uncertain etiology characterized by progressive and irreversible fibrosis of the interstitium of the lungs, which leads to dysfunction of pulmonary ventilation and air exchange, causing respiratory distress in patients. IPF is also known as a carcinoid disease.¹⁰⁴ Once a person is diagnosed with IPF, the only way to slow down the progression of the disease is to take medication. In end-stage cases, the only way to save a patient's life is through a lung transplant. Nidanib and pirfenidone are currently approved and marketed for the treatment of IPF, and patients need to take large amounts of nidanib and pirfenidone to maintain the blood levels needed for treatment. Due to the high side effects of nidanib and pirfenidone, the tolerance of the patients to the drugs is reduced and the development of the disease is accelerated.¹⁴ Alveolar type II epithelial (AT2) cells play a parthenogenetic stem cell role, which promotes alveolar regeneration by proliferating or inducing directed differentiation into alveolar type I epithelial (AT1) cells.¹⁰⁵ Considering the critical role of AT2 cells in IPF progression, maintaining AT2 stem cell identity to promote alveolization is considered a promising therapeutic strategy. Wang et al¹⁰⁶ reported an inhalable mucus-penetrating lipid nanoparticle (Figure 5A) for co-delivery of dual mRNAs to promote alveolization by restoring dryness of AT2, ultimately leading to the treatment of IPF. SP-A antibody-modified SLNPs were constructed by coupling surface-active substance protein A (SP-A) antibody to the surface of lipid nanoparticles (LNPs). SP-A is highly expressed on the surface of alveolar type II epithelial (AT2) cells. SLNPs can specifically bind to AT2 cells through SP-A antibodies, significantly improving the targeted delivery efficiency to AT2 cells. The uptake efficiency of SLNPs in the lung epithelial cell line MLE12 is significantly higher than that of unmodified LNPs. The liposome nanoparticles were able to reverse mitochondrial dysfunction by improving nicotinamide adenine dinucleotide biosynthesis, thereby inhibiting senescence in AT2 cells. Termination of pathological epithelial remodeling and fibroblast activation induced by damaged AT2 cells promotes alveolar regeneration (Figure 5B–F). SLNPs can efficiently deliver dual mRNAs encoding cytochrome b5 reductase 3 (CYB5R3) and bone morphogenetic protein 4 (BMP4) to AT2 cells, achieving precise regulation of AT2 cell function. Breast cancer anti-estrogen resistance protein 3 (Bcar3), originally discovered for its role



in estrogen resistance in breast cancer, belongs to the family of proteins of the novel Src homolog 2.¹⁰⁷ It was shown that abnormal Bcar3 levels were observed in lung tissue from IPF patients and mice with pulmonary fibrosis, and that Bcar3 expression was positively correlated with fibrotic gene expression. Zeng et al¹⁰⁸ reported a self-assembled liposome loaded with Bcar3 siRNA for the treatment of IPF. Experimental results showed that gene therapeutic agents could be delivered precisely to lung macrophages and fibroblasts by intratracheal injection of liposomes containing Bcar3 siRNA, effectively reducing the expression of Bcar3 to 59% of baseline levels. Liposome-delivered drugs for the treatment of IPF have achieved good efficacy in animals. However, no liposome-delivered drug for the treatment of IPF has entered clinical trials to date, which may be related to the rapid disease progression and short median survival of IPF patients. In future work, new liposome-delivered drugs may be explored for the treatment of IPF.

Lung Cancer

Lung cancer is one of the malignant tumors with the highest morbidity and mortality rates in the world, with 1.4 million or even 1.6 million deaths per year, accounting for 18% of all malignant tumor deaths.¹⁰⁹ Lung cancer is mainly divided into non-small cell lung cancer and small cell lung cancer. Early-stage lung cancer usually has no clinical symptoms. However, when the tumor grows to a certain extent, it is a sign that the disease has entered the intermediate and advanced stages, when obvious clinical symptoms will appear. Unfortunately, once lung cancer reaches the middle or late stage, surgery is no longer indicated in most cases, and the only way to maintain the patient's life is to seek chemotherapy or radiotherapy. When patients undergo chemotherapy, the side effects of the drugs are often too much for them to bear. Therefore, finding a feasible delivery system to accurately deliver chemotherapeutic drugs to the cancerous area can alleviate patients' pain to a certain extent. Liposome delivery of drugs for cancer treatment has been clinically effective. In this section, the efficacy of liposomal delivery of different drugs for the treatment of non-small cell lung cancer and small cell lung cancer is described and current problems are presented.

Non-Small Cell Carcinoma

According to global cancer statistics, it is estimated that more than 2 million people are newly diagnosed with lung cancer each year,¹¹⁰ of these, non-small cell lung cancer (NSCLC) accounts for 80–85%. The most common histologic subtype of NSCLC is adenocarcinoma, followed by squamous carcinoma.¹¹¹ Nearly 70% of NSCLC patients present with locally advanced or systemic metastases at the time of diagnosis.¹¹² As a result, most of the patients have lost the chance of surgery when they are diagnosed and must resort to chemotherapy to keep them alive. Chemotherapy is indicated for many lung cancer patients, and the use of conventional chemotherapeutic agents appears to have reached a therapeutic plateau.¹¹³ There is an urgent need for a new treatment for NSCLC. MMP-9 is a protease upregulated in various malignant tumors.¹¹⁴ As shown in [Figure 6A](#), Zhang et al¹¹⁵ constructed an integrated hybridized nanovesicle called cancer cell membrane liposome by fusing cancer cell membrane and charge reversal liposome membrane of MMP-9 switchable peptide. The cancer cell membrane (Cm) coated on the surface of nanoparticles (CLip-PC@CO-LC NPs) retains the surface proteins of protocancer cells (such as Pan-cadherin) and can specifically bind to non-small cell lung cancer (NSCLC) cells through homologous recognition, improving the targeted binding efficiency to tumor cells. It can accurately deliver siRNA to tumor cells with high MMP-9 expression. The highly expressed matrix metalloproteinase 9 (MMP-9) in the tumor microenvironment can cleave the MMP-9-sensitive peptides on the surface of nanoparticles, expose the positively charged cell-penetrating peptides (CPP),¹¹⁶ enhance the internalization ability of nanoparticles towards tumor cells, and achieve targeted penetration triggered by TME. The experimental results showed that due to the long blood retention time, homologous targeting ability and accumulation of tumor microenvironment activation properties of this liposome ([Figure 6D-F](#)), it could effectively inhibit the growth of tumor cells and provide a new therapeutic idea and method for the treatment of NSCLC. Despite the ability of chemotherapy and molecularly targeted therapies to slow the progression of NSCLC, the life expectancy of patients with advanced NSCLC is still less than 1 year. Abnormal expression of antibodies produced against receptors on the surface of cancer cells has emerged as a new target for cancer treatment, eg, human epidermal growth factor receptor-2 (HER-2), epidermal growth factor receptor (EGFR), heparin A2 receptor (EphA2).¹¹⁷ Ernest Moles et al¹¹⁸ reported a polyethylene glycolated liposomal adriamycin targeting EGFR. It has been shown to effectively target and inhibit the growth of NSCLC tumors in vivo while reducing drug delivery to the

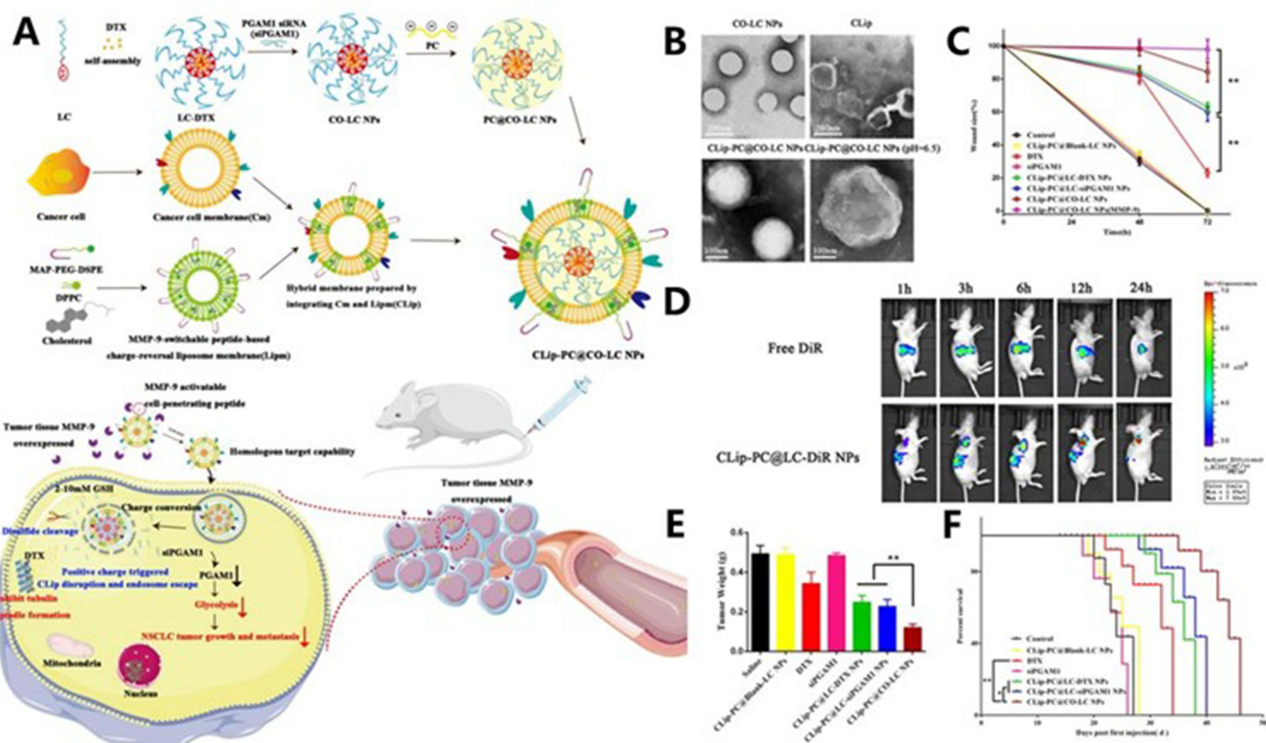


Figure 6 (A) A schematic diagram of the synthesis of CLip-PC@CO-LC NPs and the intracellular uptake. (B) Representative transmission electron microscopy (TEM) images of CO-LC NPs, CLip, CLip-PC@CO-LC NPs, and CLip-PC@CO-LC NPs (pH= 6.5) negatively stained with phosphotungstic acid (scale bars= 200 nm and 100 nm). (C) Average hydrodynamic size of CO-LC NPs, PC@CO-LC NPs, and CLip-PC@CO-LC NPs (n= 3). (D) Biodistribution of free DiR and CLip-PC@LC-DiR in A549 cell tumor-bearing nude BALB/c mice at 1, 3, 6, 12, and 24 h after administration. (E) The tumor weights of the A549 tumors excised from all groups after different treatments. Data is expressed as the mean± standard deviation (SD; n= 6). (F) Mice survival rates after different treatments (n= 6). **p* < 0.05, ***p* < 0.01, ****p* < 0.001. Modified with permission.¹¹⁵ Copyright 2021, BMC.

heart. More and more products utilizing liposomes to deliver antitumor drugs are now on the market with excellent results, but their long-term safety and stability still have not been accurately evaluated. In subsequent clinical trials, the sample size of the study should be expanded to obtain more accurate and consistent data to support the rationale for liposome delivery of antitumor drugs.

Small Cell Carcinoma

Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine tumor that accounts for approximately 13% of all lung cancer cases. SCLC is characterized by rapid growth and early metastasis. Despite significant improvements in the number and efficacy of current radiotherapy treatment regimens, treatment options and overall survival in SCLC have remained virtually unchanged for nearly three decades.¹¹⁹ The five-year survival rate for SCLC was 7.2%, whereas the five-year survival rates for adenocarcinoma, squamous cell carcinoma, and large cell carcinoma were 29.8%, 22.5%, and 18.6%, respectively.^{120,121} Although the treatment of SCLC has always been a major challenge, researchers have never stopped exploring. David R Spigel et al²⁷ conducted a clinical trial where they utilized liposomal irinotecan versus topotecan for the treatment of recurrent SCLC in adults, and out of 461 randomly assigned patients, 229 were treated with liposomal irinotecan and 232 with topotecan. The results of clinical trials have shown that the use of liposome-delivered drugs for the treatment of SCLC is effective in reducing the probability of adverse events. More importantly, liposomal delivery of drugs significantly reduces the side effects of the drugs. Because SCLC is prone to recurrence, the current study does not address whether treatment with delivery systems is effective in reducing recurrence rates. Therefore, future studies need to focus on liposomal delivery of drugs in the prognosis of SCLC.

Current Developments

How to effectively treat lung diseases has always been a topic of interest for researchers. Although traditional drug administration methods have achieved remarkable results in treating lung diseases. However, as time went by and technology advanced, the problems with traditional treatment methods became increasingly prominent. Traditional drug administration may cause the following problems. 1) Drug resistance; 2) Drug side effects; 3) Low delivery efficiency.¹²² Therefore, how to solve these problems has become the goal of the researchers. Nowadays, people have proposed using drug delivery systems to address these issues. Drug delivery systems can be classified into nano-delivery systems, hydrogel delivery systems and biological carrier delivery systems.¹²³ Liposomes, as one of the members of the nano-delivery system, have been widely applied in drug delivery due to their unique structure and excellent biocompatibility.¹²⁴ More importantly, researchers have already used liposomes to load drugs for the treatment of clinical diseases. In recent years, more researchers have utilized delivery systems to deliver drugs to the lungs with good efficacy. Liposomes are widely used in drug delivery, gene delivery, and cosmetic industry as an advantage of possessing good biosafety, strong delivery ability, and easy modification. Liposomes have two cores, a hydrophilic core and a hydrophobic core. For drugs with poor solubility and low bioavailability, the solubility and bioavailability of the drug can be greatly improved by being encapsulated in the hydrophobic core of the liposome, which in turn enhances the therapeutic efficacy of the drug. Due to the lipophilic phospholipid membrane bilayer of liposomes, it avoids being recognized by the body as a foreign substance and reduces the occurrence of a series of immune reactions. In addition, the unique structure of liposomes allows it to more easily cross the physiological barrier of the lungs to accomplish drug delivery. More importantly, in lung delivery, liposomes can be modified by antibodies, targeting peptides and cell shuttle peptides on their surface to enable more precise delivery of liposomes to the lesion site.

The intelligent responsive liposomes can adapt to the changes in the microenvironment of the disease, thereby achieving intelligent drug release, which has attracted extensive attention from researchers. Currently, there are several types of liposomes designed with different stimulus-responsive types according to the environmental changes at the lesion site. For example, pH-responsive, temperature-responsive and enzyme-responsive.

However, liposome delivery of drugs still faces several challenges and limitations.

1. The self-stabilization of liposomes still needs to be improved. Liposomes may cause structural damage due to phospholipid oxidation, hydrolysis, or phase transition during storage or in vivo circulation, triggering drug leakage.⁴⁰ At the same time, long-term preservation of liposomes usually requires freeze-drying, which is a complex process and may affect liposome integrity.
2. Preparation methods and quality of liposomes need to be improved. Conventional methods for the preparation of liposomes are difficult to sustain in large quantities, and there is a need to find a simpler method adapted to the generation of liposomes in large quantities. Liposome nanoparticles should be produced with homogeneity and consistency between batches.
3. Insufficient targeting efficiency of liposomes. Unmodified liposomes are susceptible to capture by the macrophage phagocytosis system and need to be polyethylene glycolized to prolong circulation time but may trigger accelerated blood clearance. Antibody, ligand modifications may improve targeting but may increase immunogenicity and the complex in vivo environment may mask targeting molecules. The poor penetration of liposomes in tumor cells limits, to some extent, the delivery of drugs from liposomes to cancer cells or tissues.¹²⁵
4. Drug release from liposomes is difficult to control precisely. Conventional liposomes rely on passive diffusion or membrane rupture for drug release, which may lead to premature or insufficient release. If smart response liposomes are used, it is difficult to ensure the accuracy and reliability of the stimulation conditions.
5. The biosafety of liposomes still needs to be improved. Natural phospholipids are biocompatible, but synthetic phospholipids may cause inflammatory reactions, and the use of natural phospholipids increases the cost of liposome production. Liposomes are difficult to deliver intracellularly and are susceptible to immune clearance by cells, and modification of peptides or cationic lipids is often required to avoid immune clearance; however, introduction of peptides or cationic lipids may increase cytotoxicity.

6. Inaccurate deposition location: Even if successfully inhaled, liposomes in aerosols mainly deposit in conductive gases, making it difficult to effectively reach deep lung tissue.¹²⁶
7. Individual differences and disease status impact: The respiratory physiological status of patients has significant individual differences, which significantly affect the deposition, distribution, and clearance of liposomes, making it difficult to predict and standardize treatment outcomes.¹²⁷
8. Regulatory challenges: Regulatory agencies such as FDA and EMA have strict approval requirements for new nanomedicine delivery systems, requiring detailed pharmaceutical, non-clinical, and clinical data, long development cycles, and high risks.¹⁵

With the development of science and technology, researchers have further expanded their focus on liposomes to meet future development needs. It may be expanded from the following aspects.

1. Design of intelligent responsive liposomes. Pathological microenvironment triggered release: Develop liposomes that are sensitive to the microenvironment of lung diseases, such as decreased pH, increased enzyme activity, oxidative stress, and specific inflammatory factors, to achieve precise drug release at the lesion site.¹²⁸
2. Long term sustained release and release kinetics optimization. Develop new carriers such as phase change liposomes and solid lipid nanoparticles to prolong drug retention time in the lungs (>24 hours) and reduce dosing frequency. Realize constant rapid drug release and avoid sudden release effects.¹²⁹
3. Artificial intelligence guides personalized treatment with liposomes. Algorithm predicts the relationship between lipid composition and drug release behavior, accelerating formula screening. Intelligent inhaler monitors patient usage habits and optimizes medication efficiency.

Inhalation preparations are also a highly promising method of drug administration at present. More scientific researchers have developed a strong interest in this. However, inhalation preparations also have a series of challenges and limitations. Currently, the problems faced in the production of inhaled pulmonary formulations involve multiple aspects such as technology, process, supervision and market. 1) Stability of preparation. Long-term stability issue: Inhalable powder preparations may experience activity loss during storage. For instance, although lactose - leucine formulations can slow down degradation, aerosol performance (FPF) may still decline. 2) High-cost production: The industrial production cost of inhalation preparations is higher than that of traditional dosage forms, mainly due to complex processes and equipment requirements. 3) Drug resistance issue: For inhalation therapy targeting multi-drug-resistant bacteria the problems of cold chain dependence and stability need to be addressed.¹³⁰

However, delivery of therapeutic drugs to the lungs remains a thorny issue due to the special physiological barrier structure of the lungs.¹³¹ Respiratory rate, breath-holding, humidity, wind speed and tidal volume are important factors affecting drug deposition. By understanding the characteristics of drug transport in the lungs, the mechanisms of deposition, the nature of the drug, the nature of the delivery system, the molecular basis of lung disease, and the barriers to drug delivery become the basis for the development of an efficient pulmonary drug delivery system.

Outlook

Overall, the development of liposome to treat lung diseases is an interesting research topic. Liposomes, as a commercially available delivery system, has been marketed in recent years with great economic benefits. Liposome delivery can be used not only for the treatment of lung diseases, but also for other diseases. Examples include bone repair, myocarditis and wound healing. Liposomes have a wide range of clinical applications and have been used in the treatment of various lung diseases. For example, lung cancer, pneumonia and COPD (Table 4). There is no doubt that the potential of liposomes for the treatment of lung diseases is enormous. Nucleic acids are one of the most important biological macromolecules within cells, responsible for carrying and transmitting genetic information and participating in the regulation of cell fate.¹³² In recent years, nucleic acid drugs have been used in genetic diseases, cancer, viral hepatitis, and new coronavirus infections, and are a highly promising therapeutic agent.¹³³ However, nucleic acid drugs have

several problems of their own. For example, poor stability, susceptibility to degradation, risk of immunogenicity, etc.¹³⁴ The key to the efficacy of nucleic acid drugs is their accurate delivery to diseased tissues and sites. There can be a range of problems in the delivery process.¹³⁵ These include: 1) Obstruction of extracellular barriers: extracellular matrix adsorption, immune clearance, etc.; 2) Difficulty with cellular uptake; 3) Ensure the integrity of nucleic acids. The above difficulties create difficulties for nucleic acid-based drugs to perform their normal therapeutic functions. The emergence of liposomes has provided new ideas and approaches to this challenge. In 2020, Hong et al¹⁶⁵ first used liposomal delivery of miR-34a to treat patients with advanced solid tumors, and despite the early termination of the experiment due to the premature death of the patient, it still proved that liposomes are feasible for delivery of nucleic acid-based drugs. Mutations or inactivation of the p53 pathway result in loss of p53 suppressor gene function, present in most human cancers.¹³⁶ Neil Senzer et al¹³⁷ reported a liposome nano delivery complex (SCL) for systemic tumor-targeted delivery. They completed the first phase I clinical trial using SCL nanocomplexes (SGT-53) to inhibit the tumor suppressor gene p53. Experimental results showed that minimal side effects of the complex were observed in patients with advanced solid tumors. More importantly, systemically delivered SGT-53 was not only well tolerated but also showed significant anticancer activity. In summary, liposome-delivered nucleic acid analogs have not only made some progress in research but have also achieved good results in clinical treatment. In the future work, if we can realize the efficient delivery of nucleic acid-based drugs and solve the stability problem at the same time, it will provide new ideas and methods for the treatment of different diseases, which will be a major technological innovation.

Liposomes are currently the most mainstream non-viral vectors for nucleic acid delivery, but they still face a series of challenges. For example: in terms of safety, immune response and nucleic acid stability.¹³⁸

1. The potential toxicity of liposomes themselves. Liposome components may be toxic to organs such as the liver, especially when used at high doses or repeatedly. Liposomes are mainly captured by the liver, and drugs may take effect in areas where they should not, causing side effects.
2. The self-toxicity of nucleic acid drugs. Foreign mRNA or siRNA may be recognized by the immune system, triggering unnecessary inflammatory responses, which may instead reduce the therapeutic effect.
3. The stability of nucleic acid drugs themselves. Exposed mRNA/siRNA is highly prone to rapid decomposition and failure in the blood. Liposome encapsulation provides protection, but incomplete encapsulation or leakage can still lead to degradation, which in turn affects the therapeutic effect.¹³⁹
4. The delivery efficiency still needs to be improved. Most of the encapsulated drugs may still be degraded by lysosomes within the cells, while only a small portion can successfully escape into the cytoplasm where they need to function and exert their effects.
5. The storage conditions are extremely strict. Liposome delivery of nucleic acid drugs requires extremely strict transportation and storage conditions. This might have led to a further increase in the difficulty of industrialization.

Aerosol refers to a complex mixed system formed by the stable suspension of tiny solid or liquid particles in a gas.¹⁴⁰ Lungs have a huge surface area and rich blood vessels, drugs are absorbed quickly. Delivering drugs to specific locations in the lungs by inhaling aerosols can, to a certain extent, avoid the first-pass effect of drugs.¹⁴¹ The deposition sites of drug particles in the respiratory tract can be controlled by adjusting the physical properties such as the size, density and shape of aerosol particles. The deposition sites of drug particles in the respiratory tract can be controlled by adjusting the physical properties such as the size, density and shape of aerosol particles. For instance, adjusting the particle size of aerosols to 1–5 μm can enable drugs to reach the trachea, bronchi and bronchioles. Meanwhile, if the particle size is less than 1 μm , the particles can reach the alveoli and may even be exhaled. Shraddha S Ghodke et al¹⁴² developed a spray-dried DPI formulation to improve solubility, stability and lung delivery of curcumin-loaded CS-HA double-coated micro colloidal particles for the treatment of lung cancer. The optimized DPI demonstrates excellent aerodynamic characteristics and is suitable for targeted pulmonary drug delivery in non-small cell lung cancer. Primary bronchial cancer accounts for almost 20% of all cancer deaths worldwide. Magnetic aerosol drug targeting is an emerging lung cancer treatment technology with enormous potential. Mohammad K D Manshadi et al¹⁴³ found that after adding permanent magnets beside tumors, for particles with a diameter of 7 μm , the particle deposition rate on the cancer was as high as

49%. Optimizing the magnet size can increase the particle deposition rate by 68%. In conclusion, the method of aerosol targeted drug delivery can effectively treat lung diseases. However, there are also a series of challenges and limitations in using aerosols to treat lung diseases.

1. Low deposition efficiency: A large portion of the drug will be lost within the device, in the oropharynx or exhaled. The proportion of drugs reaching the target lung area is limited.
2. Safety concerns: Inhaled particles or carriers may cause local irritation, inflammation or immune responses. The long-term pulmonary toxicity of nanomaterials still requires in-depth research.
3. Industrialization and regulatory challenges: The development and production processes of inhalation products are complex, and the quality control requirements are strict, resulting in high costs. The bioequivalent evaluation of inhalation products by regulatory authorities is also highly challenging.

To sum up, both liposome delivery of nucleic acids and aerosol targeting of the lungs present opportunities and challenges. In the future, these problems should be addressed in a targeted manner to accelerate clinical transformation.

Data Sharing Statement

The dataset supporting this review article is included within all the cited article.

Consent for Publication

We have included 3 Figs (Figures 4–6) from previously published literature with required copyright permission from the copyright owners. We have mentioned this in the manuscript with appropriate citations.

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Author Contributions

All authors made a significant contribution to the manuscripts reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the manuscripts; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

These authors declare no conflicts of interest in this work.

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