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Pulmonary inhalation for disease treatment: Basic research and clinical translations

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ABSTRACT

Pulmonary drug delivery has the advantages of being rapid, efficient, and well-targeted, with few systemic side effects. In addition, it is non-invasive and has good patient compliance, making it a highly promising drug delivery mode. However, there have been limited studies on drug delivery via pulmonary inhalation compared with oral and intravenous modes. This paper summarizes the basic research and clinical translation of pulmonary inhalation drug delivery for the treatment of diseases and provides insights into the latest advances in pulmonary drug delivery. The paper discusses the processing methods for pulmonary drug delivery, drug carriers (with a focus on various types of nanoparticles), delivery devices, and applications in pulmonary diseases and treatment of systemic diseases (e.g., COVID-19, inhaled vaccines, diagnosis of the diseases, and diabetes mellitus) with an updated summary of recent research advances. Furthermore, this paper describes the applications and recent progress in pulmonary drug delivery for lung diseases and expands the use of pulmonary drugs for other systemic diseases.

1. Introduction

The primary objective of the drug delivery system is to "release the drug at the appropriate time and concentration at the specified target" [1]. Pharmaceutical research has long focused on the synthesis and discovery of highly effective pharmacologically active compounds for the treatment of relevant diseases; however, the efficacy of a drug is not linear and is closely related to the drug and mode of delivery. A drug delivery system is defined as a device or formulation that introduces a drug into the body and enhances its efficacy and safety by controlling the timing, location, and rate of release, a process that involves the use of the drug, the release of the active ingredient, and the passage of the active ingredient across a biological barrier to the site of action [2]. Therefore, it is particularly important to release the right concentration of drug at the right time and place, which not only prolongs the duration of action of the drug but also allows for further modifications to achieve targeted delivery to specific locations to increase the local concentration at specific locations and reduce the amount of drug administered while also achieving the desired therapeutic effect. The physicochemical properties of the medicinal substance and the biological barriers (such as organ membranes and skin) often define the prerequisites for effective drug delivery [3]. Such as pharmacokinetics, distribution, cellular uptake and metabolism, excretion and clearance, and even drug toxicity. In addition, changes in the environment (moisture, temperature, and pH) may affect the pharmacological activity of a drug during storage or *in vivo*. Many drug delivery modes have been developed; the oral route of drug administration is a classical and widespread mode for treating severe or persistent disorders. However, the biggest drawback of oral drug delivery is its low bioavailability. Similarly, intravenous drug delivery has been a classical mode, which delivers drugs directly to the body and can improve bioavailability; however, poorly water-soluble drugs cannot be delivered intravenously, and most anti-tumor drugs are refractory. In addition, intravenous delivery is hemolytic and cytotoxic, and its dose should be strictly controlled. In transdermal drug delivery, drugs are applied to the surface of the skin, where they are diffused, absorbed, circulated, and transported to the target tissue [4].

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Specifically, after transdermal drug delivery, the drug is stabilized during passive diffusion with neutral molecules across the stratum corneum into the interfollicular region [5]. The drug then diffuses to the target organ, affecting the corresponding tissues and producing a therapeutic effect, before being excreted into circulation. Transdermal delivery is an attractive alternative to oral administration that allows for earlier drug metabolism when there is a significant first-pass effect, non-invasive compared with intravenous delivery, less painful, and allows for self-administration [6]. Examples of drugs delivered using transdermal delivery include benzoyl peroxide for acne, hydrocortisone for dermatitis, and neomycin for superficial infections [7]. In addition to the treatment of skin diseases, transdermal drug delivery can also be used to treat diabetes by delivering insulin [8]. This method of delivering insulin, in addition to the above advantages, can provide sustained release to maintain therapeutic concentrations for longer periods [9]. Nevertheless, the passive transport of higher molecular weight protein drugs, such as insulin (>500 Da), is significantly limited [10]. High cost, low permeability limits, low drug levels in blood or plasma, variation in barrier function (age and site), and molecular size restriction (<500 Da) are challenges that remain to be addressed in transdermal drug delivery [7]. Intraocular administration is a method of drug delivery that delivers a drug solution into the conjunctival sac to achieve therapeutic or adjunctive diagnostic effects such as local cleansing, anti-inflammation, astringency, anesthesia, and pupil dilation or constriction. Clinically, topical eye drops are the most effective and simplest method of ocular drug delivery as they reach the ocular surface directly and are less invasive [11]. Topical eye drops are widely used for the treatment of intraocular diseases, but the bioavailability of intraocular medications is very low, mainly due to drainage of the medication by the nasolacrimal duct and clearance by tears. Furthermore, patient compliance with the dosing regimen is poor [11]. Biomolecules hold great promise for intraocular therapy; however, it is difficult for topical eye drops to penetrate the eye because of their unique physiologic barriers. Another intraocular drug delivery technique, intraocular injections, can resolve this problem, as can intravitreal and subretinal injections. However, frequent injections increase the risk of some complications such as retinal detachment, cataracts, vitreous hemorrhage, and endophthalmitis, and poor patient compliance remains unresolved [12]. Intranasal drug delivery is a mode of administration in which drugs are applied to the nasal cavity to exert local or systemic therapeutic effects. Early intranasal administration was generally limited to the treatment of localized symptoms such as seasonal rhinitis or respiratory infections [13]. Due to its advantages of convenient drug delivery, rich vascularity of the nasal mucosa, high absorption rate, and targeted action, intranasal drug delivery has been used in the treatment of systemic diseases, such as the insulin treatment of diabetes mellitus [14]. Meanwhile, because intranasal drug delivery has the advantage of bypassing the blood-brain barrier, this route can also be used for targeted delivery to the brain [15]. However, intranasal administration has the disadvantage of having low stability due to the short residence time of the drug because of mucosal cilia clearance and drainage, enzymatic actions, and changes in nasal anatomy [14]. For some biomolecules, there may also be an increased risk of nasal injury [14], and long-term use may increase the risk of tumors [16]. Pulmonary drug delivery, a non-invasive technique for local and systemic applications, has attracted attention owing to its several benefits over conventional drug delivery techniques.

The delivery of specific drugs directly to the lungs or using the lungs as a medium for the active or passive inhalation of drugs by patients to treat local or systemic diseases is collectively termed the pulmonary drug delivery system. This system is the most direct and effective route of drug delivery for the treatment of pulmonary diseases and a localized way that can directly and rapidly increase the concentration of drugs at the treatment site and reduce systemic concentrations. For some drugs with systemic therapeutic effects, due to the large number of alveoli in the lungs (300–400 million epithelial cells, the total area of which can reach 70–100 m^2), the number of capillaries is extremely high, blood flow is abundant, and capillaries with high permeability are distributed in the adjacent alveoli between the two layers of epithelial cell membranes so that the drugs are easily absorbed through the surface of the alveoli into circulation and can exert a systemic therapeutic effect at the same time. Pulmonary drug delivery offers many advantages over traditional routes (e.g., oral and intravenous), including [17,18]: 1) possible higher concentrations of targeted pulmonary drug delivery; 2) lower drug doses are required, with fewer side effects; 3) rations of targeted pulmonary drug delivery are possible; 4) suitable for drugs that are first sensitive to the intestine and/or liver, avoiding gastric absorption and portal circulation; 5) faster onset of action (e.g., fentanyl and morphine); 6) a non-invasive invasive with a low risk of infection compared with intravenous [19] and intramuscular [20,21] injections.

Pulmonary inhalation is an ancient mode of drug use. Approximately 4000 years ago, plants containing substances such as scopolamine and atropine were burned and inhaled to produce "mysterious" effects with narcotic and hallucinogenic effects. Ancient Egyptians employed the vapor of the Hyoscyamus Niger plant to treat patients with respiratory distress in the 1500s, the earliest recorded reference to medicinal aerosol delivery [22]. In the mid-19th century, the original nebulizer produced pressure from its handle, which nebulized the liquid medicine through the nozzle. Handheld and early electric nebulizers were developed between 1930 and 1950 to help patients with asthma get epinephrine into their airways. In 1956, the first pressure dosing inhaler (pMDI) was developed in Riker's laboratory for delivering epinephrine or isoprenaline. Furthermore, in 1971, the first dry powder inhaler (DPI)—Spinhaler, was introduced. It was first used to deliver sodium propylene glycol, followed by salbutamol. Soft mist inhalation devices (SMIs) were released early in the new millennium. They employ a multi-dose device, emit a gradual, persistent mist, and do not require hand-to-mouth coordination. The key points in the history of the development of inhalation drug delivery are summarized in Fig. 1. Many inhalation formulations have been approved for marketing by the Food and Drug Administration, and according to the different inhalation formulations, they are divided into aerosol, inhalation powder, inhalation spray, inhalation liquid, and transformable vapor formulations. Aerosols, dry powder inhalation, and inhalational agents are the most common. The advantages and disadvantages of pulmonary drug delivery are summarized in Table 1.

Pulmonary inhalation has been investigated; however, fewer data on drug delivery via pulmonary inhalation are available compared with oral and intravenous deliveries; therefore, this review discusses the basic research and clinical translation of pulmonary inhalation drug delivery for the treatment of diseases and provides insights into the latest advances in pulmonary drug delivery. In the first half of this review, we discuss the pharmacokinetic mechanisms of the lungs in terms of physiological structure and barriers and summarize the advantages and disadvantages of the old and new processing methods, drug carriers (with a focus on various types of nanoparticles (NPs)), and different delivery devices for pulmonary drug delivery. In the second half of this review, we focus on the applications and advances of pulmonary drug delivery in clinical settings, such as COVID-19, asthma, lung infections, lung cancer, and other pulmonary diseases; furthermore, inhaled vaccines, diagnosis of diseases, and treatment of other systemic diseases (e.g., diabetes mellitus and neurological disorders) are also discussed. In the final section of this review, we present some of the products for pulmonary drug delivery available on the market and summarize some remaining challenges that must be addressed to improve inhalation drug delivery in the lungs.

2. Airway and lung anatomy and physiological functions

2.1. Airway and lung structures

The respiratory tract begins at the nasopharynx and oropharynx, passes through the trachea and bronchial regions, and ends at the

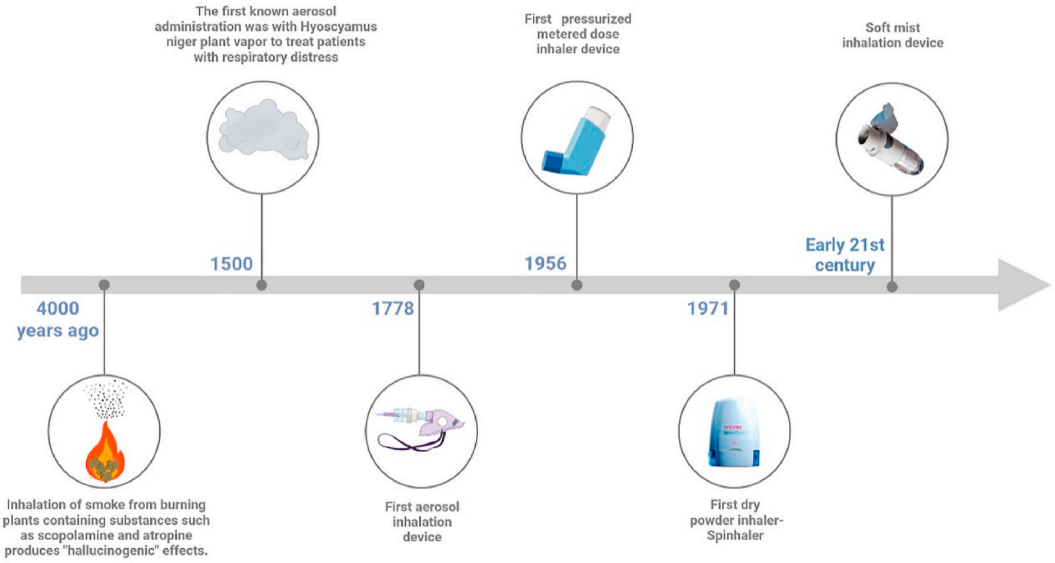

Fig. 1. History of pulmonary drug delivery.

Table 1
Advantages and disadvantages of pulmonary drug delivery.

	Elements	Ref
Advantages	1. No first-pass effect of the liver.	[23–25]
	2. High bioavailability, reduced drug utilization dose and reduced side effects.	[17,26,27]
	3. Large alveolar surface area, fast absorption, rapid onset of action.	[17,25,28]
	4. Non-invasive and low risk of infection.	[19,21]
	5. Continuous drug release.	[29,30]
Disadvantages	1. pH stability and enzyme degradation.	[23]
	2. Physiologically tolerated components.	[23]
	3. Particle size and aerodynamic behavior.	[31,32]
	4. Regulatory and formulation requirements.	[33,34]
	5. May cause lung disease.	[35,36]

alveoli. The primary purpose of the respiratory system is gas transport and exchange. The lungs are the primary organs of the respiratory system, with one organ on each side. The two lungs are similar but not perfectly symmetrical; the left lung is smaller and narrower than the right lung. The right lung consists of three lobes separated by two fissures, while the left lung consists of two lobes separated by an oblique fissure. The root of each lung is called the hilum, which connects the lungs to the heart and the trachea [37]. Typically, the structure of the lungs begins with the trachea and the main bronchi, which are divided into left and right bronchi on either side of the lung and connect to smaller bronchi that lead to the fine bronchi and eventually to the terminal and respiratory bronchi. On average, the bronchial tree contains ~23 generations of airways, ranging from ~17 (upper lobe segments) to ~32 (posterior basal segments). The first ~10 generations are bronchi, followed by ~4 generations of conducting bronchioles and ~4 generations of respiratory bronchioles. The small airway trees distal to the terminal fine bronchi are called alveoli and represent the functional and respiratory units of the lung parenchyma [37,38]. This structure also greatly increases the surface area of the lungs and airways, which facilitates the exchange and absorption of substances. An anatomical drawing of a mouse lung illustrates the structure (Fig. 2). Differences exist in the total alveolar area between males and females. Although males and females have the same mean alveolar size, males have a larger alveolar surface area and total alveolar number due to a larger total lung volume [39]. The lungs have a large surface area, extensive vascular distribution, rich blood supply, and low enzymatic activity [17]. These characteristics favor drug absorption in the lungs.

2.2. Physiological barriers in the airways and lungs

Mucus-cilia clearance and macrophage phagocytosis are the two primary mechanisms of lung clearance of xenobiotics [41]. Mucus-cilia clearance is the primary defense mechanism of the airway and functions primarily by removing particles >5 μm in size. Alveolar macrophages (AM) may phagocytose tiny particles that enter the alveolar region; However, this depends on the particle size. For example, 1.5–3 μm is the best particle size for macrophage phagocytosis, and that of particles <1 μm or >5 μm is poor [41,42]. In addition, the macrophage phagocytic rate is much lower than that of mucus-cilia clearance [43]. Similarly, the degradation and catalysis of various enzymes is a lung clearance mechanism. The process of respiratory mucosal immunization is illustrated in Fig. 3A.

2.2.1. Physical mechanism

During airway conduction, fine particles are primarily removed by mucosal cilia clearance, a lung protection mechanism against bacterial and dust particles [41]. To capture foreign pathogens inhaled and facilitate their removal by mucociliary clearance, airway mucus functions as a complex viscoelastic gel, creating a protective physical barrier and shielding the airway epithelium [44]. The mucus covers all the wet epithelium of the airway, and the viscoelastic mucus network captures and removes inhaled material and oscillates toward the pharynx via mucus cilia [45]. The clearance rate of mucus and particles from cilia reportedly increases with the airway diameter; therefore, this process is fastest in larger airways [46]. The endothelial fluid of the lung, comprising mucus ranging from 5 to 10 μm in thickness, 3 % solids, and 97 % water, is a protective barrier for the lower epithelial cells [42]. Mucosal cilia clearance may be reduced owing to increased mucus layer thickness or higher mucus viscosity [47] and is most effective for particles >6 μm [48]. Previous studies have shown that approximately 90 % of inhaled coarse particulates (>6 μm) are removed within 24 h [42]. The distribution of tiny particles in the lungs after inhalation is illustrated in Fig. 3B.

2.2.2. Cellular mechanisms

In the lung, macrophages are the most abundant immune cells during homeostasis, with a high degree of heterogeneity and high levels of plasticity [49]. Macrophages have a range of functions in the lungs, including maintenance of homeostasis, immunosurveillance, removal of cellular debris, repair, clearance of microorganisms, and elimination of

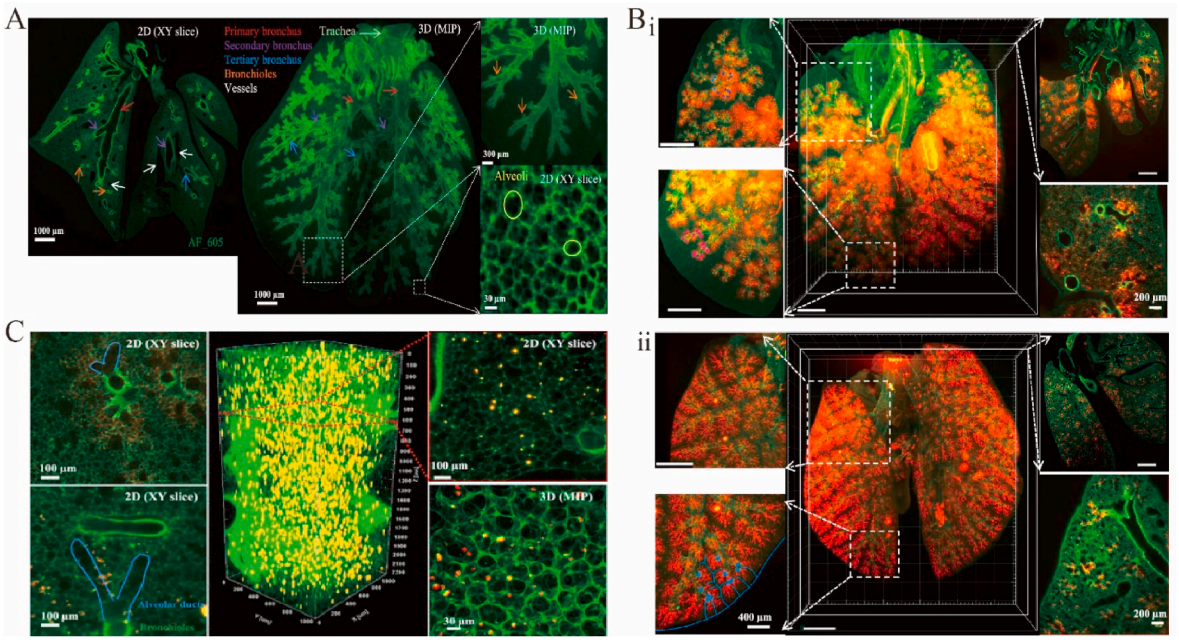

Fig. 2. Lung anatomy of mouse (A) 3D reconstruction of mouse's lungs. Adapted reprinted with permission from Ref. [40]. Copyright © 2019 American Chemical Society. (B) 3D reconstruction of the distribution of melamine resin NPs in mouse lungs following pulmonary NP delivery via rapid pressing of a syringe plunger (i) and inhalation (ii). Adapted reprinted with permission from Ref. [40]. Copyright © 2019 American Chemical Society. (C) NP deposition (red or yellow) with alveolar tissue structure (autofluorescence, green) during mouse lung contraction and inflation. Adapted reprinted with permission from Ref. [40]. Copyright © 2019 American Chemical Society. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

inflammation [50]. Depending on where they are found, macrophages present in the alveoli and airways are commonly referred to as AM, while those in the interstitium are called interstitial macrophages (IM) [51]. It has been reported that in the lungs of mice, AM are far more numerous larger, and have more prominent pseudopods than IM [49]. AM are among the first cells to encounter the complex environment of dust, organic matter, pollutants, and pathogens, and play a key role in initiating and resolving inflammatory and immune responses, as well as distinguishing between harmless and potentially lethal AGS [52]. The function of IM remains unclear. A previous study has shown that IMs increase the ability to produce IL-10 in a steady state, a feature that suggests that IMs may have a regulatory role [53]. Furthermore, IMs are classified into two or three subsets. For example, based on steady-state IM expression of CD11c and MHCII, IMs are further classified into three subgroups—IM1 (CD11clowMHCIIlow IMs), IM2 (CD11clowMHCIIhigh IMs), and IM3 (CD11chighMHCIIhigh IMs). In mice, Chakarov et al. have identified two separate IM populations using single-cell RNA sequencing. The Lyve1lowMHCIIhigh IMs subset is predominantly found around the fine bronchial nerve bundles, whereas The Lyve1highMHCIIlow IMs is around the pulmonary vasculature [54]. In addition, Gibbings et al. suggested a level of heterogeneity in lung IMs by characterizing three phenotypically distinct IM subpopulations [55]. Particles in the upper part of the respiratory tract are cleared mainly by the oscillation of mucosal cilia. Conversely, the AM is responsible for the degradation and elimination of fine particles deposited deep in the lungs [56,57]. AMs are noticeable at the periphery because they can eliminate tiny particles of size 1.5–3 μm [58]. Notably, macrophage phagocytosis is much less efficient than the clearance mechanism of mucus cilia and can be almost entirely excluded for inhaled drug particles in the 0.5–1.5 μm range [33,59].

2.2.3. Chemical mechanism

Although numerous metabolic enzymes are present in the alveolar cells, they have lower metabolic rates than their counterparts in the gastrointestinal tract and liver [60,61]. However, some enzymes have specific functions in the lungs. For example, superoxide dismutase is found in AM and lung endothelial fluid [62]. AM and alveolar epithelial cells contain the lysosomal enzymes cathepsin B, H, and L [14]. Similarly, specific immune factors such as lysozymes and complements are present in airway secretions and kill inhaled microorganisms. Cytochrome P450 is likewise present, and cytochrome P450 is the primary enzyme family catalyzing oxidative biotransformation. This enzyme acts in the metabolism of most drugs [63].

2.3. Metabolism of inhaled drugs in the airways and lungs

Drug pharmacokinetics after inhalation in the lungs diverge more than those of oral or intravenous administration. There are unique interactions between the drug and the pulmonary biological barrier. The bioavailability of the drug in the lungs is determined by the role of drug deposition. Most drug deposition occurs in the alveolar cavity, conducting airway, and oropharynx [41]. The ratio of drug deposition is related to the inhalation device, inhalation flow rate, disease-related factors, and drug particle size [41]. The second factor is the dissolution of the drug in the lungs, which depends on the chemical and physical properties of the medicine, physiological factors, and the medicine formulation [33]. Third, the structure of the respiratory tract and the characteristics of the drug affect its absorption in the lungs. Drugs are absorbed more rapidly in the alveolar cavity than in the airways [64]. Lipophilic medicines are quickly absorbed after dissolution via passive cross-cellular diffusion in the epithelial cells [65]. The fourth aspect is the retention and metabolism in the lungs. The primary variable influencing drug retention in the lungs may be its tissue affinity or tissue partition coefficient [33]. Although pulmonary metabolism depends primarily on the enzymes in the lungs, the metabolic capacity of pulmonary enzymes is lower than that of the gastrointestinal tract and liver. The fifth aspect involves the mechanism of mucosal ciliary clearance in the lungs. The ciliary movement of mucus allows for drugs delivered by the lungs to return to the oropharynx [66], affecting drug bioavailability. Finally, moving a drug from the lung tissue to the blood circulation [41]. In contrast to other lung regions, absorption clearance occurs faster in the alveoli owing to their vast absorption surface, thin

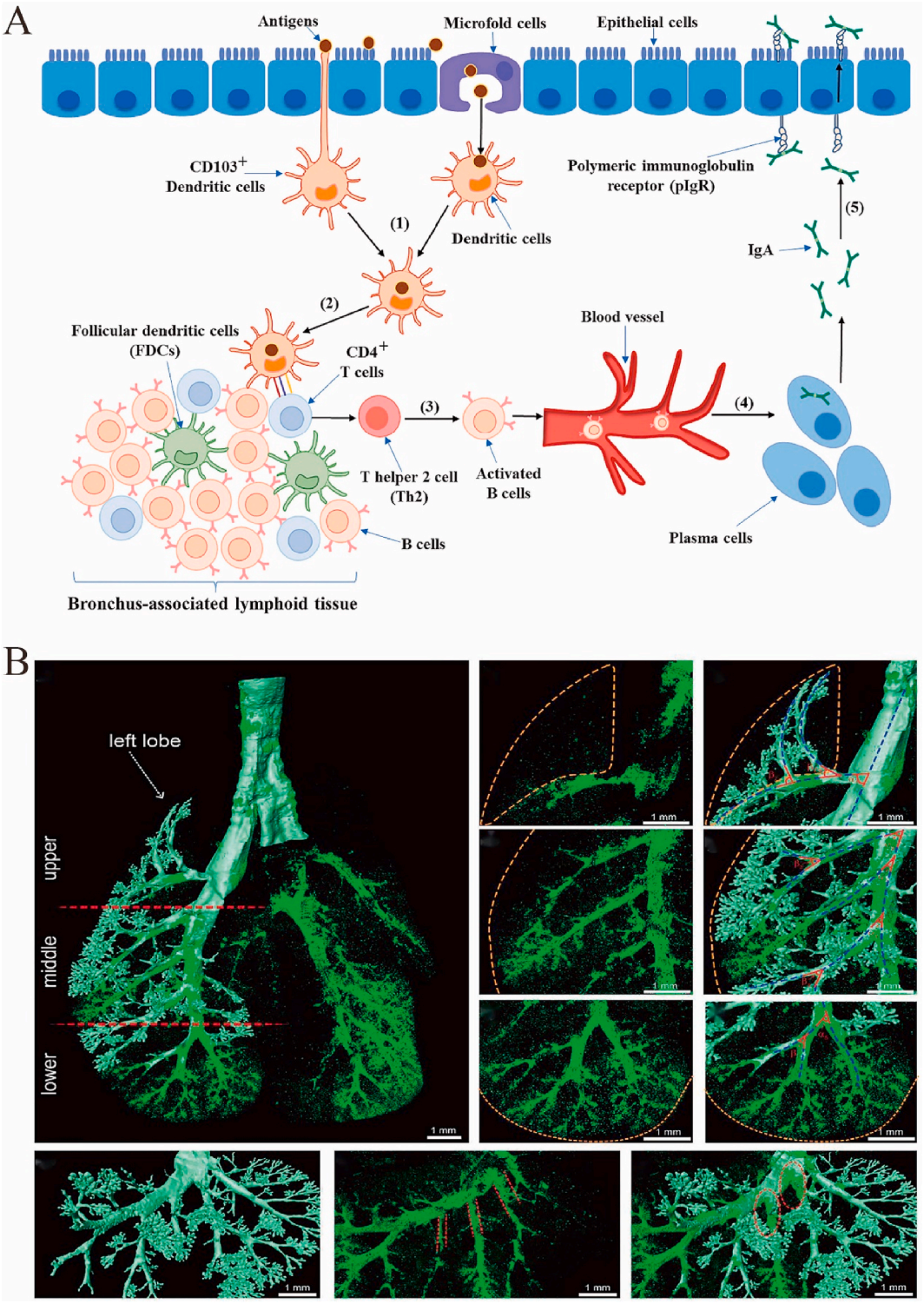

Fig. 3. Mechanism of pulmonary inhalation drug delivery (A) Schematic diagram of respiratory mucosal immunity. Adapted reprinted with permission from Ref. [69](License number: 5,682,871,319,855). (B) Distribution of Alex Fluorescence 488-labeled cross-linked γ-cyclodextrin metal-organic framework particles in the left lung after inhalation. Adapted reprinted with permission from Ref. [70], based on CC BY License.

epithelium, and pulmonary circulation supply [64,67]. The ideal pulmonary drug delivery system should enable sustained drug release through delayed pulmonary clearance mechanisms and effective lung deposition to maintain prolonged therapeutic drug concentrations [68]. Therefore, these aspects should be investigated in pulmonary drug delivery systems to improve drug bioavailability.

3. Delivery devices and processing technology for pulmonary drug delivery

The formulation of pulmonary drug delivery involves combining different principles of aerosol-generating devices and the corresponding drug forms into a pharmacological combination of products; the type of drug delivery and absorption efficiency depends on different devices and

reagent processing methods. In this section, we introduce some process innovations and the latest progress in delivery devices, the processing technology of pharmaceutical agents, and the material carrier of the formulation.

3.1. Devices for pulmonary drug delivery

Approximately 4000 years ago, smoke or vapor was produced by heating drugs in jars or pipes to treat asthma-related diseases. Advanced devices and optimal formulations are required to obtain optimal lung deposition, and drug formulations and delivery devices should be optimally coordinated to achieve targeted deposition. The primary devices used for pulmonary drug delivery include dry powder inhalers (DPIs) (Fig. 4A), pressurized metered-dose inhalers (pMDIs) (Fig. 4B), and nebulizers (Fig. 4C). Other new, efficient, and available delivery devices include SMI (Fig. 4D) and smart inhaler devices (Fig. 4E). To achieve optimal intrapulmonary drug distribution and deposition, patients should follow certain criteria when using the inhaler, including the three components: pre-inhalation, inhalation start, and post-inhalation. When using pMDIs, DPIs, or SMIs, patients should exhale slowly and deeply before inhalation, that is, to be in the possible functional residual position to obtain the maximum inspiratory volume at the beginning of inhalation, to hold their breath as much as possible after inhalation (approximately 10 s is better), and exhale slowly to facilitate full drug distribution and deposition in the lungs. However, the internal resistance differs for different devices and requires further investigation. For example, the internal resistance for pMDIs and SMIs is generally low; however, that between different DPIs is higher. A brief comparison between different inhalers is shown in Table 2.

3.1.1. pMDI

Of the available inhalation units, pMDI is the most used worldwide, with an estimated annual production of over 500 million units [88]. The structural components of a conventional pMDI device include a bite, an actuator, a dosing valve, and a canister bottle [89]. The bottle body primarily comprises inert materials, including glass, stainless steel, aluminum, and plastic, to withstand the high pressure of the propellant gas when it remains in a liquid state [79]. The dosing valve provides a precise volume of aerosol at each use, approximately 20–100 μL, and includes internal and external valves. Within pMDI, the driver consists of an expansion chamber and a nozzle (driver orifice). The size of both the expansion chamber and the driver orifice affects the spray pattern and the size of the particles emitted [90]. The pMDI device is used in treating chronic obstructive pulmonary disease (COPD) and asthma, with the advantages of portability, low cost, simple operation, stable dose, and accurate dose. However, it requires high hand-to-mouth coordination abilities of patients, and improper operation decreases drug action efficiency in the lungs [73]. pMDI formulations can be classified as solutions or suspensions, depending on whether the drug is in solution or solid form [91]. pMDI is used as corticosteroids to deliver DNA [92], proteins [93], and viral vaccines or phages [94]. The ideal propellant would be non-toxic, non-flammable, compatible with the formulation, and maintain constant pressure throughout the lifespan of the product [73]. pMDI propellants previously contained chlorofluorocarbons [79]. They are, however, currently banned owing to environmental pollution concerns. Fluoroalkanes (HFA) can be used as alternatives; However, the shift in propellant from chlorofluorocarbons (CFCs) to HFA brings about a new set of challenges for pMDI. The use of high-pressure HFA makes the physical and chemical properties of the drug within pMDI unstable (frosting or precipitation), which in turn may lead to dosage changes [34]. This would be unsuitable for the delivery of some drugs, such as biologics, as their dose range per application is small [95]. This, therefore, requires the design of new dosing valves and excipients [60]. In addition, the common propellants HFA-227 and HFA-134a are not suitable for some poorly soluble drugs, since they clog the nozzle and inhomogeneous suspension of the drug [72].Adding carbon dioxide

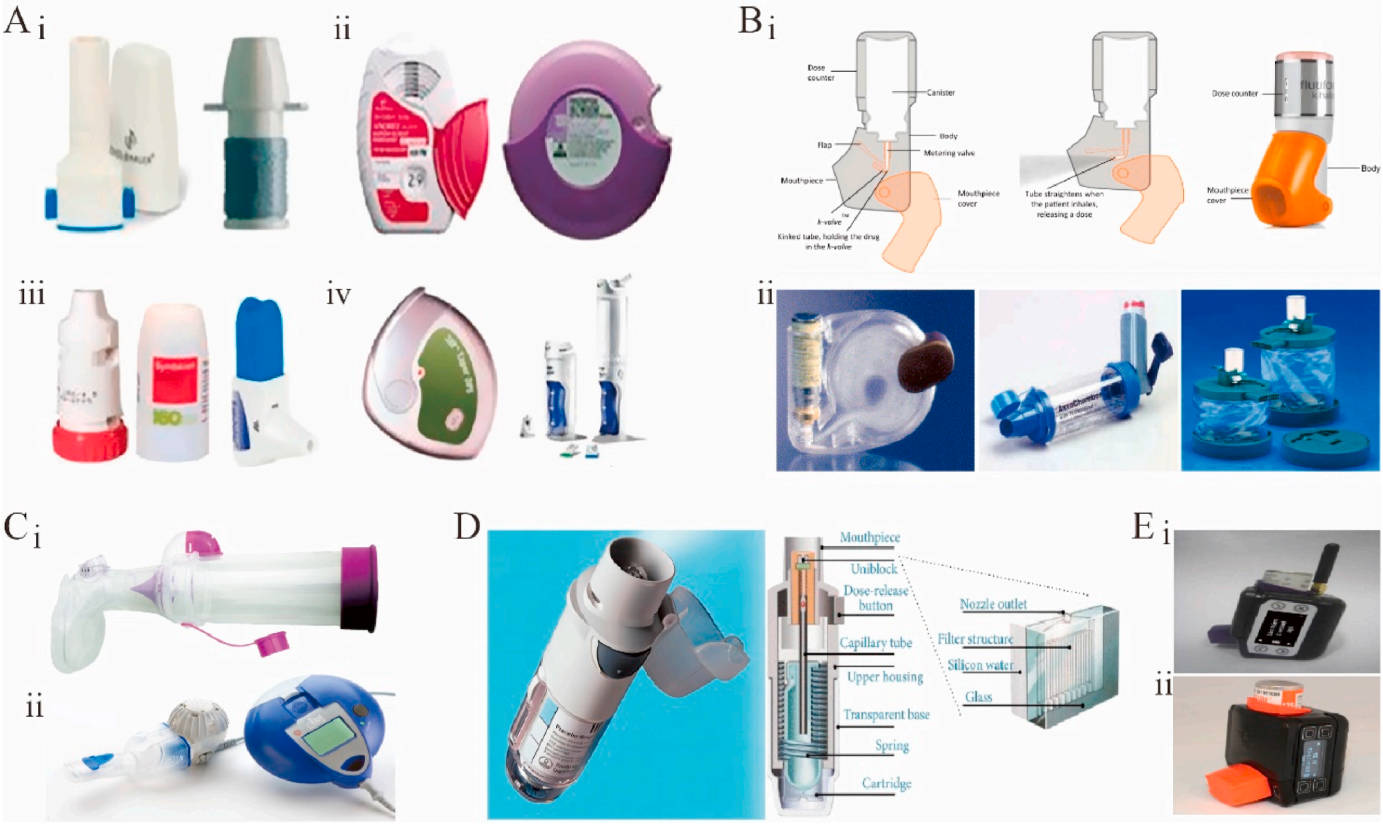

Fig. 4. Devices for pulmonary drug delivery (A) Different generations of DPI.

Table 2
Comparison of pulmonary drug delivery inhalation devices.

	pMDI	DPI	Nebulizers	SMI	Ref
Pharmacological form	Liquid	Dry powder	Liquid	Liquid	[43]
Advantages	1) Portability 2) Relatively inexpensive 3) Relatively easy to operate 4) Stable and precise dosage, more suitable for large dosage administration 5) Multi-dose device	1) Portability 2) Breath-actuated; no need for patient hand-mouth coordination 3) No propellant is required.	1) Simple operation 2) Simple drug dosage forms and a wide variety of drugs can be delivered. 3) Most devices are inexpensive and easily accessible 4) There is no need for patient hand-mouth coordination, and it can be used at any age	1) Portability 2) High rate of drug deposition in the lungs 3) Can be recommended for patients with poor respiratory coordination 4) Multi-dose device	[25,27, 71–76]
Disadvantages	1) Requires patient hand-mouth coordination 2) Requires propellant and may generate contamination (e.g., Freons) 3) Not respiratory-driven	1) Complex manufacturing process 2) The need for specific drug dosage forms 3) Complex pre-dose handling 4) The need to minimize the suction flow	1) Difficult to carry 2) Long time for drug administration 3) Risk of bacterial contamination during drug administration 4) Low efficiency of drug delivery 5) New nebulizers are expensive	1) Complex process of use 2) High cost 3) Small application area	[72,73, 77–81]
Applications	Various respiratory diseases, such as lung cancer, asthma, COPD, lung infections, tuberculosis, etc.	Various respiratory diseases such as lung cancer, asthma, COPD, lung infections, tuberculosis, etc., immunizations, diabetes mellitus	Various respiratory diseases, such as lung cancer, asthma, COPD, lung infections, tuberculosis, etc.	Primarily suitable for outpatient use in patients with COPD or asthma	[72, 82–87]

(CO_2) to HFA-134a and ethanol not only improves the drug wettability but also the particle size distribution, perhaps as a new propellant system [96]. In addition, HFA-152a can be used as a new propellant [97]. The new pMDI is categorized as a respiratory drive and auxiliary coordination device. The respiratory-driven Maxair AutohalerTM, Easi-Breathe inhaler®, and K-haler® are less demanding for the patient and can alleviate hand-to-mouth coordination challenges than traditional pMDI devices [73,98]. Ancillary coordination devices include spacers and valve-holding chambers (VHCs), which modulate the effectiveness of aerosol delivery. A spacer is a tube or extension positioned where the patient and the PMDI meet. At the biting end, the VHC is a one-way valve that permits breathing while obstructing exhalation from entering the chamber. This inhalation facilitates increased deep lung deposition while decreasing oropharyngeal deposition by slowing the velocity of the expelled aerosol and allowing the propellant to evaporate from larger droplets. Electrostatic deposition reduces the dose delivered by pMDIs [99]. A new generation of assistive coordination devices can determine whether a patient is correctly inhaling, such as a spacer that whistles when a patient inhales too quickly [100]. This design may be helpful for special populations, such as the elderly and children. Even though pMDI has several advantages and many improvements have been made, hand-to-mouth coordination remains a significant challenge hindering its utility.

3.1.2. DPI device

DPIs are portable devices, also known as inhalation powder nebulizers, which are preparations of solid micronized DPI alone or mixed with a suitable carrier such as capsules, vesicles, or multi-dose reservoirs. They are used with a specially designed DPI where the patient actively inhales the nebulized drug into the lungs. Although DPI drug formulations are chemically more stable than liquid formulations, their production is challenging [80]. The design of the inhalation device and powder formulation determine the DPI performance. The DPI design focuses on balancing the resistance and flow rate of the inhaler. A high-velocity airflow allows for more frequent and stronger impingement of the agent to increase particle depolymerization and achieve higher fine particle fractions. However, fast airflow can cause more deposition of the agent in the oropharynx and reduce the drug dose delivered to the lungs [101]. In addition, DPIs are unsuitable for patients with dyspnea or COPD, and they can be passive or active, depending on the method of powder atomization [73]. Passive DPIs do not provide energy and rely solely on the airflow generated by inhalation as the driving force for nebulizing the micronized powder of the drug. The primary challenge with passive DPIs is that patients might be hindered from generating sufficient inspiratory flow rate to ensure the delivery of adequate and uniform doses, failing to achieve the desired efficacy. Active DPIs were built with an internal energy source to ensure that the medication distribution was independent of the inspiratory flow rate of the patient. This power source may be a battery, compressed gas, or spring mechanism [73]. Passive DPIs are further divided into single- and multi-dose devices; with a single-dose DPI, the device can be reused, reducing costs. The drug needs continuous refilling, and the operation is more complicated, increasing the chance of patient error, particularly in older adults. Moreover, these drugs are prone to contamination and the possibility of misuse. Single-dose Spinhaler™ and Rotahaler™ devices were the first available passive DPI products [102].

These limitations are not associated with the multiple-dose types. The Multi-Unit Dose DPI uses factory-measured and hermetically sealed packages of doses; hence, one unit can simultaneously hold multiple doses without reloading [73]. However, they require certain mechanisms to prevent drug overdose. The primary types of multidose DPIs are reservoir-type multidose drug delivery devices and unit-type multidose drug delivery devices. The Reservoir-Based DPI is a non-premeasured, multi-dose dry powder inhaler where the powder is mixed and filled into the reservoir of the inhaler; a single inhalation of the powder is measured and made available for the patient to inhale by rotating or pressing the metering unit on the inhaler. This method avoids repeated loading of drugs; however the accuracy and uniformity of the dose per administration and the stability of the drug in the reservoir remain major challenged. The first true reservoir-based inhaler, the Turbuhaler, was introduced in 1988 for delivering budesonide and formoterol fumarate. The FDA has since approved several reservoir-type inhalers, including TEVA's Respiclick, AZ's Flexhaler, Pressair, Novartis' Certihaler, and Organon's Twisthaler. DPIs are respiratory-actuated devices triggered by the patient's inhalation at the appropriate time and, hence, require no hand-breath coordination to minimize patient error; however, the efficiency and consistency of drug delivery and aerosol dispersion may rely on the patient's inspiratory flow rate [103,104]. A unitary multi-dose DPI is a powdered medication dispensed into individual blisters, disks, grooves, or strips, which are then combined into a dry powder inhaler device. In addition to eliminating the need for repeated refilling of the medication, Novolizer, a new multi-dose

refillable DPI, features a triggered-flow valve system and several feedback mechanisms, which ensures proper inhalation by the patient and adequate lung deposition, thereby improving patient compliance. Novolizer is also suitable for use in patients with reduced inspiratory flow rates, including the elderly, small children, and patients with pulmonary disease [105].

3.1.3. Nebulizer device

A nebulizer is a device that converts a drug solution or suspension into an aerosol and delivers it to the lower respiratory tract. Nebulizers do not require active patient cooperation; therefore, they are useful for children, older adults, unconscious patients, and those who cannot use pMDIs or DPIs [73]. However, nebulizers should be installed, loaded with the medication, disassembled, and cleaned after use. This can be challenging for untrained older adults and children [27]. Nebulizers can be used for tidal breathing and be adapted for critically ill patients [76]. Compared with pMDIs and DPIs, nebulizer liquid formulations are less expensive and simpler to create. In addition, nebulizers allow for the simultaneous delivery of multiple drugs. In addition, nebulizers can deliver higher doses than pMDIs and DPIs; however, the delivery takes longer [78]. Jet nebulizers function based on the Venturi principle and Bernoulli effect [77]. The gas flow moves rapidly through a small capillary tube, generating a low pressure that drives the liquid upward in the capillary to atomize [106]. This nebulizer is suitable for delivering solutions and suspensions and can deliver anti-microbial, liposomes, and recombinant cells that pMDIs and DPIs cannot deliver. The primary challenge with spray nebulizers is the need for bulky compressors to generate aerosols, which simultaneously generate noise and decrease the liquid temperature of the nebulizer chamber [83]. Some reports have classified jet nebulizers into four types: jet nebulizers with bellows, jet nebulizers with collection bags, breath-enhanced jet nebulizers, and breath-driven jet nebulizers [77]. Jet nebulizers with bellows are conventional constant-output nebulizers that produce a continuous aerosol during inhalation, exhalation, and breath-holding. The aerosol produced during exhalation is stored in the collection bag and is provided to the patient during the next inhalation through a one-way valve located between the mouthpiece and the collection bag. Breath-enhancing jet nebulizers release more aerosol during inhalation through a one-way valve in the bite and utilize the negative pressure created by the patient's inhalation to generate aerosols. The breath actuates the jet nebulizer, sensing the patient's inspiratory flow and delivering the aerosol only during inhalation. As ultrasonic nebulizers use high-frequency vibrations of electrical pulses to generate aerosols and are suitable for delivering low-viscosity solutions and not for nebulizing heat-sensitive and protein-based drugs [107]. They are divided into two categories: (1) large-volume ultrasonic nebulizers and (2) small-volume ultrasonic nebulizers. Large-volume ultrasonic nebulizers are most commonly used to deliver hypertonic saline for sputum induction, whereas small-volume ultrasonic nebulizers are used to deliver inhaled medications [77].Since ultrasonic nebulizers require a power source for charging, their portability is inferior to that of jet nebulizers. Recent improvements in nebulizer technology have led to the development of mesh nebulizers that use micropump technology for aerosol production. They force a liquid drug through multiple holes in a mesh or perforated plate to produce an aerosol. Mesh nebulizers can be divided into two categories, namely active and passive mesh nebulizers. Active mesh nebulizers use a piezoelectric element that contracts and expands upon the application of an electric current and vibrates a precisely drilled mesh in contact with the drug to produce an aerosol. Passive mesh nebulizers use a transducer horn that induces passive vibrations in a perforated plate with 6000 tapered holes to produce aerosols. Vibrating-screen nebulizers are powered by batteries or micropump technology and require a micron-sized vibrating mesh to produce aerosols. They have the advantages of low power consumption, no noise, easy portability, short nebulization treatment time, high output efficiency, a small margin, and an adjustable dose. Vibrating-mesh nebulizers significantly reduce the drug delivery time and lower the required therapeutic dose [108]. Lung deposition is approximately two to three times higher with a mesh nebulizer compared with jet nebulizers [109]. Due to the greater efficiency of the mesh nebulizer, patients' clinical response should be monitored during treatment to prevent side effects. However, viscous drugs and suspensions can clog their orifices, thereby reducing the nebulization efficiency of the drug, requiring cleaning and maintenance, and complicating its use for patients. In comparison to the PARI LC® jet plus or Respironics SideStream® jet nebulizers, studies have shown that the Omron U22 vibrating screen nebulizer greatly decreases drug residues in the nebulizer, which is particularly advantageous for expensive pharmaceuticals [110].

3.1.4. SMI

The SMI, a modern inhalation device that produces a slow, long-lasting aerosol that reduces drug deposition in the oropharynx when inhaled by the patient is a small, portable, handheld device requiring no power source. Its power primarily relies on the mechanical power of the spring, and no liquid gas propellant is required. In contrast to pMDI, SMI helps to harmonize drive and inhalation and does not require patients to exceed the inspiratory flow threshold for DPI. Therefore, SMI can overcome the difficulties patients may experience with pMDI and DPI [111]. The only currently available SMI is the Respimat®. The Respimat is propelled by a compression spring in the base, which forces the drug solution through a tiny nozzle at an angle that causes it to converge and form an inhalable mist of slow-moving particles that the patient inhales slowly and deeply. Compared with pMDIs, SMIs emit soft mist at a rate of approximately one-tenth its speed. Furthermore, to coordinate the inhalation of the patient with the actuation of the device, the SMI soft mist is produced for a long (approximately 1.5 s) and contains a high proportion of fine particles (approximately 65–80 %) [112]. All these features reduce the drug deposition in the oropharynx, increasing that in the lungs. Compared with pMDIs and DPIs, SMIs considerably boost the lung deposition rate, lowering the therapeutic dose [27]. This inhaler has a similar portability to the pMDI or DPI, thus, suitable for outpatient use in patients with COPD or asthma. The SMI has been suggested as an inhaler for people with inadequate coordination and inspiratory flow rate [73]. However, it has certain disadvantages, including being more complex to use, and it is the most common challenge occurring during preparation. Only 2.7 % of patients with COPD could accurately complete all steps in this trial, and nearly 77.0 % could not use the device on their first attempt and required assistance from a healthcare provider or other caregiver [81]. In addition, to conserve medication, most patients fail to release enough aerosol to saturate the channels of the device before the first use to ensure dose consistency [81].

3.1.5. Intelligent inhalation device

To meet specific market demands, the use of smart technologies has increased. In particular, digital systems have been applied in various types of inhalation devices, including digital DPIs, MDIs, nebulizers, and next-generation SMIs. Digitization can help to provide patient-centered care practical solutions for patients, healthcare providers, and pharmaceutical companies [113].Smart inhalers are electronic monitoring systems that use a connection to the Internet or other devices. Inhalation data are stored in solid-state memory for later retrieval via a personal computer [72]. Smart inhalation device function involves using monitoring systems to improve patient compliance and reduce medication errors caused by devices or patient handling through external or self-integration [72]. For example, the Electronic Breezhaler® is a built-in smart inhaler that tracks, communicates, and senses usage information. Original integrated and add-on devices are the two primary categories of smart inhalers. Additional devices can transform traditional inhalers into smart ones to improve patient compliance [114], such as CareTRx™ and SmartTrack (an early version of Hailie™) [115, 116]. Indeed, medication adherence has been reported to increase by

180 % with the use of SmartTrack [116]. Electronic Breezhaler®, a new smart device for dry powder inhalation, integrates electronic devices that sense, record, and communicate usage data [117]. MDILog™, Doser™, Smart Inhaler Tracker, Smart Mist®, and Smart Track™ were the first MDIs to be digitized, featuring new recordings of the date and time of start-up along with specific reminders via ringtones [118]. Instant feedback is also provided when using the Digitized MDIs, such as a red light when inhaling too fast, green when inhaling too slowly, and no display when suction is too weak. The Propeller® add-on device is embedded with a Global Positioning System (GPS) feature that detects the exact location where the patient is experiencing an acute asthma attack, and maps the patient's risk for possible asthma triggers [118]. Propeller® additional sensors are compatible with various pMDIs such as Flovent® and Ventolin® HFA [119]. In addition, Propeller®, approved by the FDA in 2018, can be used on DPIs [120]. Enerzair® Breezhaler®, approved for asthma treatment in the European Union in 2020 [121], consists of a Propeller® sensor and records the sound of breathing during inhalation along with the driving sound of the rotating capsule [113]. The HeroTracker Sensor class B digital device, in combination with the Diskus® DPI, reminds patients to comply with the treatment program. In addition, inhalation movements can be recorded and monitored via a Bluetooth connection [113]. The ProAir®Digihaler®, an all-in-one digital DPI with built-in sensors and Bluetooth technology, can be used to treat patients aged $\geq$4 years with reversible obstructive airway disease [122]. In 2020, Respiro was integrated into the RS01 single-dose DPI [123]. Respiro tracks medication use, automatically detects and records patient-generated inhalation parameters (e.g., inhalation flow rate and duration) [123]. These digitized inhalation devices offer tremendous advantages in preventing patient use errors and improving patient compliance [113]. In addition, physicians can also track treatment status and patient compliance with the treatment program in real-time, thus preventing the disease from worsening and improving patients' quality of life [113]. Nonetheless, smart energy inhalation devices can be more expensive than traditional devices. In addition, patient privacy and security should be considered [72]. The complex approval process for bringing digital respiratory devices to market remains a global issue [113].

Devices: (i) First generation: breath-actuated single unit-dose devices. They provide a fine particle fraction of approximately 10–20 %. (ii-iii) Second generation: breath-actuated devices:(i)Multi-unit devices and (ii)Multi-dose devices. They provide a fine particle fraction of approximately 20–40 %. (iii) Third generation: provides a higher fine particle fraction. Adapted reprinted with permission from Refs. [75,124], based on CC BY License. (B) pMDI and auxiliary equipment. (i) k-haler® device. Adapted reprinted with permission from Ref. [98], based on CC BY License. (ii)gasket and holding chamber with valve. Adapted reprinted with permission from Ref. [112], based on CC BY License. (C) Different kinds of nebulizers.(i) InspiraMask Atomizer (ii) The eFlow (PARI, Midlothian, VA) is a vibrating mesh nebulizer. Adapted reprinted with permission from Ref. [83] (License number: 5,681,700,253,495). (D) The Respimat soft mist inhaler. Adapted reprinted with permission from Ref. [125] (License number: 5,681,720,072,475). (E) (i)(ii) SmartTrack inhalation device. Adapted reprinted with permission from Refs. [115,116] (License number: 5,681,721,229,961 and 5,681,730,615,912).

3.2. Processing method for pulmonary drug preparations

3.2.1. Co-suspension technology

Co-suspension delivery, also known as the inhalation phospholipid microsphere technology, is a new processing technology for drug formulations in pMDI devices. It involves using low-density porous phospholipid particles to adsorb drugs of different densities (e.g., micronized drug crystals) to provide stable, uniform, and easily dispersed suspensions, ensuring stable dose delivery, effectively avoiding inconsistent drug delivery caused by irregularities in the pMDI device operation (e.g., insufficient shaking) and improving the proportion of drug deposition in the lungs. Using drug particles alone or in conjunction with one or more medications is enabled by co-suspension procedures [91]. Another benefit of the co-suspension technique is that the particles are evenly distributed, allowing greater drug delivery to the lower respiratory tract while reducing oropharyngeal exposure [126,127]. Regardless of the differences in inspiratory flow rates or patient misuse and mishandling of the pMDI device, the co-suspension delivery technique allows for consistent drug deposition rates [128]. Recent studies have confirmed that inhaled drugs can be deposited uniformly in the lungs after 3 and 10 s breath-holding when delivered in a co-suspension [129]. The suspension delivery technique addresses some critical formulation challenges affecting suspended MDIs and can be applied to drugs or drug combinations with different physicochemical properties at different concentrations [34]. Whether co-suspended with micronized drug crystals [34] or when a drug is added to a pellet [130], other excipients such as co-solvents or suspension stabilizers are no longer required because the porous particles spontaneously form a physically stable and easily dispersed suspension in the HFA propellant. Three complications in the pMDI can be solved using co-suspension technology: 1) inaccurate delivery of ultralow doses of drugs, 2) dose dependence of drug delivery efficiency, and 3) drug delivery with a higher fine particle fraction compared with single drug suspensions [34].

3.2.2. Inhalation particle preparation technology

According to aerodynamics, the particle size of a lung-delivered formulation is a critical factor influencing local drug deposition in the lungs [31]. Aerosol dosages of less than 3 μm were reportedly strongly correlated with whole-lung deposition [131]. From a particle-engineering perspective, the particle shape, diameter, and density of the drug affect the lung deposition rate [72]. Needle-shaped particles have a higher shape factor than spherical particles, resulting in smaller aerodynamic diameters [132]. The methods for preparing respirable particles include top-down and bottom-up techniques. Top-down techniques include micronization and traditional grinding methods (ball mills, colloid mills, hammer mills, and airflow pulverization). Bottom-up techniques include spray freeze drying and supercritical fluids [133]. The chosen preparation technique affects the solid state of the powder, which can potentially modulate atomization and atomization stability [134]. The spray freeze-drying technique has been used to create inhalable particles of nucleic acid medications, influenza vaccinations, protein-peptide pharmaceuticals, and small molecules such as Technosphere® and PulmoSphereTM. This combines the benefits of freeze-drying and spray-drying.

3.2.2.1. PulmoSphereTM. PulmoSphere™ is a technology that allows for the creation of spongy particles with a high surface area, which can significantly improve drug delivery efficiency and dose consistency [72]. This technology involves using an emulsification spray-drying process to prepare small porous sponge-like particles composed of phospholipids [135]. The particles consist of two endogenous materials for the lungs, namely distearoyl phosphatidylcholine (DSPC) and calcium chloride in a molar ratio of 2:1 [136]. Phosphatidylcholine (also known as lecithin) is the main lipid component of the surface-active substances on the surface of the human lung. Calcium ions are thought to interact with the phosphate portion of the choline phosphate headgroup in DSPC, resulting in a bulk powder with higher environmental robustness [135]. The density of particles generated based on the PulmoSphere technique is 0.01–0.50 g/cm^3 [137].The preparation of the raw material, atomization into liquid droplets, drying to produce small particles, and collection of these particles are the four steps of spray drying (Fig. 5A) [135]. From a particle design point of view, two key characteristic times determine the morphology and distribution of solid components within spray-dried particles, namely the time required for the droplet to dry by convection and the time required for the

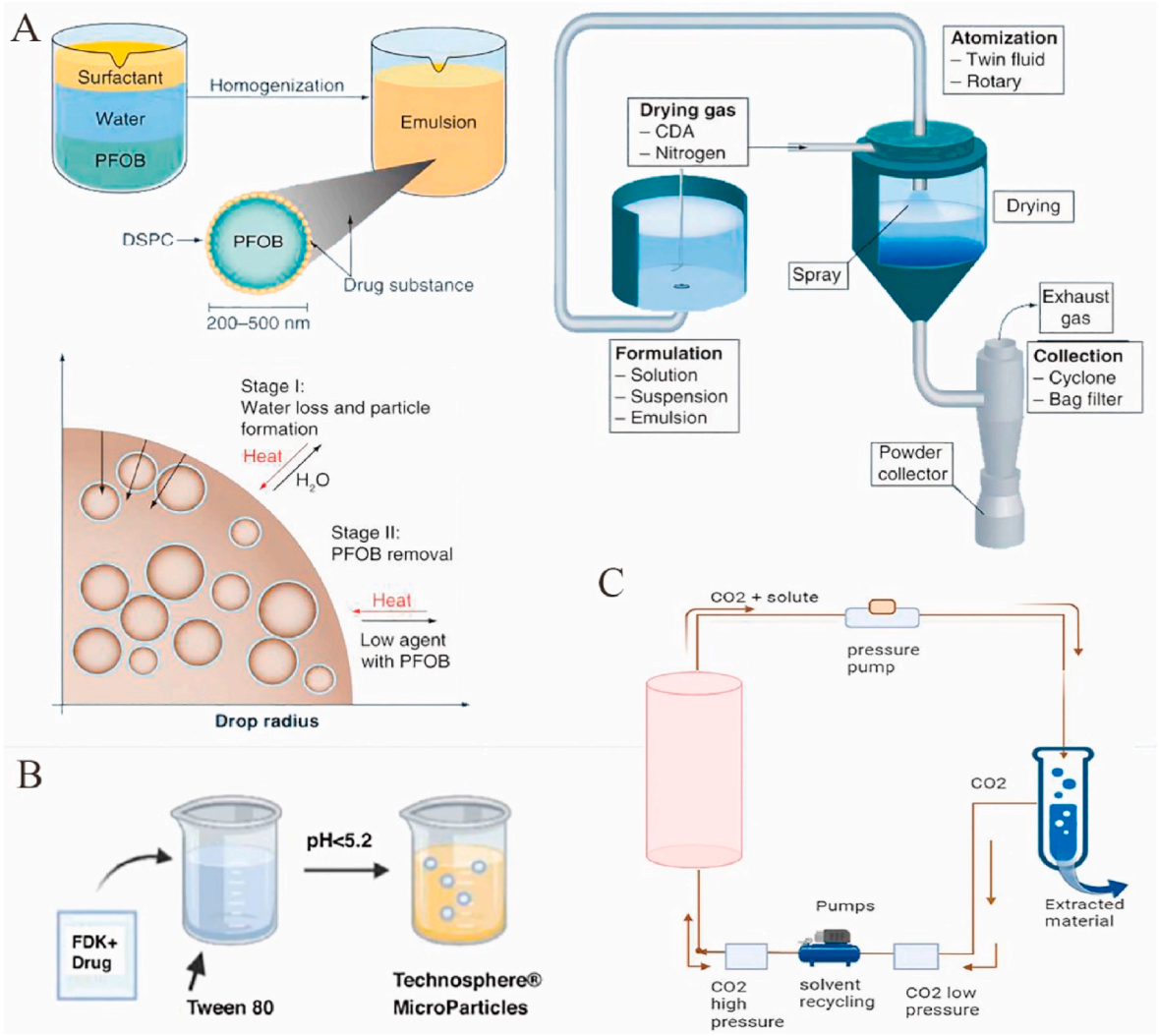

Fig. 5. Schematic diagram of some processing techniques for pulmonary drug delivery (A) PulmoSphere™ pellets manufactured using an emulsion-based spray drying process: sub-micron oil-in-water emulsion droplets are produced via high-pressure homogenization, followed by drying of the atomized droplets with clean, dry air at elevated temperatures and collection of the dried particles in a dryer. In the first stage of drying, the slowly spreading emulsion droplets are enriched on the surface of the evaporated droplets, eventually forming a shell at the interface. In the second stage, the oil phase evaporates through the particle shell, leaving behind pores. Adapted reprinted with permission from Ref. [135] (License number: 1423095-1). (B) Technosphere® technique: proteins and peptides were added to a slightly acidic solution containing fumaryldiketopiperazine (FDKP), and during precipitation the particles were microencapsulated in FDKP microspheres. The prepared microspheres were then freeze-dried to convert them into a powder suitable for inhalation. Adapted reprinted with permission from Ref. [23](License number: 5,681,930,063,936). (C) Flow of supercritical fluid extraction: The tiny particles within the fluid are first diffused using an electrostatic mixer, and supercritical CO_2, which has been heated to the procedural temperature, is injected through another inlet located at the top of the vessel. The liquid solution and the supercritical anti-solvent are simultaneously fed into the precipitator in either the downflow or counterflow modes. Adapted reprinted with permission from Ref. [157] (License number: 5,681,930,766,701).

dissolved or dispersed components to diffuse from the edges of the atomized droplet to its center [138]. The ratio of these two characteristic times defines the Peclet number (*Pe*). If $Pe \ll 1$, the composition in the atomized droplet has sufficient time to diffuse throughout the evaporated droplet and eventually forms a uniform composition throughout the particle. If $Pe \gg 1$, low-density particles with a core/shell component distribution will occur, and slow-diffusing emulsion droplets (i.e., DSPC and $CaCl_2$) will be enriched on the surface of the particles. DSPC enrichment can be achieved using an atomized droplet with a core/shell component distribution [138].The hydrophobic surface formed by the DSPC enrichment helps to reduce the inter-particle cohesion of PulmoSphere powders, which in turn results in excellent powder fluidization and dispersion of PulmoSphere aerosols [139,140]. Active pharmaceutical ingredients can be incorporated into PulmoSphere™ formulations in carrier-, suspension-, and solution-based. Based on this, PulmoSphere® formulations are available in three forms: solution-based, suspension-based, and carrier-based formulations [137]. Porous core-shell morphological characteristics, processing aids, and excipients of the PulmoSphere™ technology are retained in any of the forms [135]. The volume percentage of the oil phase in the emulsion feedstock can be changed to alter the microcrystalline characteristics of solution-based PulmoSphere powders [141]. TOBI® Podhaler® is the first FDA-approved product produced using solution-based PulmoSphere® technology. The dispersed Pharmaceutical active ingredient (API) particles in suspension-based PulmoSphere™ formulations can be crystalline or amorphous. The drug is incorporated into the suspension of raw material in the form of fine particles [142]. Amorphous drugs or crystalline particles are coated with excipients, resulting in individual particles [135]. An inhalable dry powder of ciprofloxacin was developed using this suspension-based form [143,144]. Small porous PulmoSphere™ particles are carriers in carrier-based formulations that create ordered mixes with micronized API [34,145]. The production of the

carrier-based form of PulmoSphere® is a two-step process: PulmoSphere® carrier fabrication and co-suspension of micronized drug with the carrier in a non-solvent [135]. The use of porous particles in the form of carrier-based PulmoSphere® has been reported to facilitate uniform distribution of pMDI drugs [146]. Bevespi Aerosphere® is the carrier-based PulmoSphere® produced for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. Drugs prepared using PulmoSphere™ technology can be delivered to the respiratory tract through various systems [135]. PulmoSphere™ technology can be used to deliver high-dose anti-microbial (up to > 100 mg) and low-dose compounded formulations (<1 μg) for asthma or COPD [147]. Using PulmoSphere™ technology, over 60 APIs have been created [135]. The PulmoSphere™ technology has some limitations; for example, adding carbohydrates to solution-based formulations may reduce the phase transition temperature of distearoylphosphatidylcholine, limiting the process parameters and causing a less stable formulation. However, the technology has many uses and requires further research and improvement.

3.2.2.2. Technosphere®. Technosphere® is a technology used to produce large surface areas and high internal porosity, resulting in low-density powders [148].Technosphere® is a drug delivery platform for treatment via the pulmonary route that involves using fumaryl diketopiperazine (FDKP, an excipient that intercalates through hydrogen bonds in a slightly acidic medium) as a solvent to form 2–5-μm-sized particles [149]. A schematic of Technosphere® technology can be seen in Fig. 5B. During the formation of FDKP microparticles, proteins, and peptides are added, which can be encapsulated into the FDKP microparticles, followed by freeze-drying to create an inhalation-safe powder. Technosphere technology produces formulations that bypass hepatic first-pass metabolism and degradation in peripheral circulation, improving bioavailability and patient compliance [150]. Insulins prepared with Technosphere® have a higher bioavailability than conventional insulins, are more effective in lowering blood glucose levels, and have a favorable safety profile [151]. MannKind's Afrezza inhaled insulin product, developed using Technosphere® technology, was approved for marketing by the FDA on June 27, 2014. Insulin supplied via an inhaler is 22–25 % more bioavailable and is removed more quickly than regular insulin, facilitating the maintenance of postprandial glucose levels [23].

3.2.2.3. Supercritical fluid technology. Supercritical fluid technology is a new process that involves using supercritical fluids, which exhibit the unique properties of liquids (solvency and negligible surface tension) and gases (transport properties) above their critical point [152]; it can be a liquid or gas. Supercritical fluid technology is suitable for various processes such as solubilization of insoluble drugs, surface modification, polymer plasticization, nano-size and nanocrystal modification, and chromatographic extraction [152]. Carbon dioxide (CO_2) is used as a supercritical fluid because of its low critical point, safety, and economical properties [23]. Supercritical CO_2 technology allows for the production of low-viscosity, low-agglomerated particles, thus facilitating drug deposition in the lungs. There are several techniques involving superfluids, such as the rapid expansion of supercritical solutions, gaseous anti-solvent processes, and aerosol solvent extraction systems [152]. The rapid Expansion of the supercritical solutions method is based on polymer supersaturation and nucleation, which occur when a polymer solution dissolved in a supercritical fluid passes through an orifice [152]. The basic concept of the gas antisolvent process is to saturate a polar solvent containing a dissolved substrate with $scCO_2$, which reduces the solvency of the polar solvent and results in the precipitation of the substrate [153]. Aerosol solvent extraction systems involve dissolving the drug and polymer in an organic solvent and spraying that solvent into the $scCO_2$ medium. The organic solvent is selected in such a way that it is soluble in $scCO_2$. The solvent is then extracted, leading to the formation of particles [152]. A schematic of supercritical fluid technology can be seen in Fig. 5C. Supercritical fluid technology has the advantage of being able to improve the solubility of poorly water-soluble drugs, in addition to moderate temperatures and rapid one-step processing [152]. It is an effective alternative method for the preparation of solid dispersions and microspheres [154].Micronization is the process of shrinking solid API to produce micron-sized particles. Additionally, the formulation of the active ingredient should be stable within the micron range to transport the medication to the lungs. Similarly, ipratropium bromide [155] and terbutaline sulfate [156] have been micronized and applied in supercritical fluid technology.

Drug particle size control is crucial in drug production and is used in drug-related production. Drug micronization, engineered particles, and crystallization technologies have gradually advanced, effectively improving the challenges for drug particle size control. However, its recognition will take time owing to cost and technical barriers.

3.3. Design principles and mechanisms for pulmonary drug delivery devices and formulations

In pulmonary drug delivery systems, the efficiency of inhaled drugs depends largely on the efficiency of drug deposition in the lungs [158]. Drug particles that fail to reach the lungs and are deposited in the oropharynx will be swallowed into the gastrointestinal tract [33], those drug particles that reach the lungs but fail to be deposited will subsequently be exhaled [64]. A fundamental characteristic that determines the site and efficiency of drug deposition is the aerodynamic diameter (d_a) [159], which is expressed as follows: $d_a = d_e\sqrt{\frac{p}{p_0 x}}$. where de is the equivalent volume diameter, ρ is the spherical particle density, P_0 is the unit density, and X is the dynamic shape factor. The aerodynamic diameter is influenced by particle size, shape, and density. Particles >5 μm tend to be deposited in the oropharynx, whereas those <0.5 μm are easily exhaled. A particle size range of 0.5–5 μm is optimal for inhalation therapy [41]. Conversely, for particle shape, acicular particles have a higher form factor than spherical particles, resulting in a smaller aerodynamic diameter [132]. However, needle-like particles can significantly affect the particle-to-particle contact area, resulting in poor powder dispersion [132]. In addition, current pharmaceutical processes hinder the manufacturing of non-spherical particles with reproducible size control [72]. At the same particle size, porous particles can reduce the density of particles. Furthermore, porous particles can evade cellular uptake by macrophages and deposit in deep lung tissue [23]. New formulation technologies,such as PulmoSphere™, are well-positioned to achieve optimal particle size distribution and better control of agent morphology and porosity [23]. The properties of the aerodynamic diameter are, at a deeper level, associated with the action of forces. Inertial impacts affect coarse particles with large masses moving at high speeds [160]. Interception affects small-diameter and elongated-shaped particles [161]. Gravitational settling affects fine particles (0.5–5 μm) with little effect on ultrafine particles (<0.5 μm) [162]. Brownian diffusion mainly affects ultrafine particles (<0.5 μm) [43]. In addition, the charge on the surface of the agent particles is another factor that influences settling; indeed, Charged particles tend to settle faster than neutral ones [163]. Inhalation devices facilitate the effective delivery of formulations to the target site, and those for pulmonary delivery are designed to emit small particles (aerodynamic diameter 1–5 μm), thereby maximizing the pulmonary dose and proportion of particles successfully delivered to the target site [164]. The faster the inhalation rate, the more deposition in the central and oropharyngeal regions, while the slower the inhalation rate, the more deposition in the periphery [41]. Several powder formulations for inhalation with particles in the micron or nanometer range tend to adhere to other surfaces or even their own surfaces, leading to their deposition in the oropharyngeal

region [165]. Therefore, de-agglomeration remains important. The dispersion mechanisms controlled by inhalation devices are primarily generated by collisions between coalescers and the device wall, collisions between coalescers, and turbulence [166,167]; this directly affects agglomeration. The higher the resistance of the DPI device, the more turbulence is generated within the device and the least disruption to the patient [168]. In addition, the nozzle of the inhalation device can significantly affect drug retention in the inhaler and deposition in the oropharynx [43]. Notably, patients' use of inhalation devices is another factor that influences treatment outcomes. For example, pMDI device activation, which requires coordination between patient inhalations, is difficult for patients who are either elderly or small children [169]. For some DPIs, patients are required to drive the inhaled powder through a certain inspiratory volume, which, for some with lung disease, is a difficult task [169]. Therefore, in addition to aerodynamic particle size factors, portability, and simplicity of operation should also be considered when designing inhalation devices. Table 3 summarizes the parameters to be considered when designing an effective inhalation device. In conclusion, different inhalation devices are used for different formulations; only by developing the correct formulation and selecting the correct inhaler can effective pulmonary drug delivery and good therapeutic results be achieved.

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4. Delivery system for pulmonary drug delivery

4.1. Drug delivery systems for pulmonary drug delivery

Some drugs (e.g., antibiotics, anti-cancer agents, and anti-asthma drugs) directly used for pulmonary delivery sometimes have challenges overcoming the airway biological and drug deposition barriers, resulting in poor therapeutic efficacy. Delivering drugs encapsulated in carriers is an effective way to address these challenges. The effective pulmonary deposition of drug-loaded inhaled particle carriers is a prerequisite for the therapeutic efficacy of drugs delivered via inhalation [70]. Pulmonary delivery of drugs via carrier-loaded drugs can deliver some drugs to the lungs or systemically, achieving controlled slow-release, improved bioavailability, and targeted transport. Carriers include traditional liposomes, NPs, and micro hydrogels. Additionally, pulmonary surfactants have been suggested as powerful medication delivery systems for inhalation therapy [170].

4.1.1. Liposomes

Conventional liposomes are studied dosage forms and have extended drug half-life, good biocompatibility, and high versatility, making them suitable carriers for drug delivery systems [171–173]. However, conventional liposomes frequently lack stability, restricting their use and application outside the intravenous route [174]. The active substance on the alveolar surface is dipalmitoyl phosphatidylcholine. Therefore, the advantages of liposomes regarding drug encapsulation and physicochemical properties could reduce irritation and damage to the lungs, likely contributing to pulmonary drug delivery. Tetraether lipids, when constituting more than 50 % of the formulation, can enhance liposome stability, sterilize them by autoclaving, provide considerable advantages for clinical applications, and facilitate pulmonary drug delivery [174]. The movement of liposomes as carriers of inhaled formulations in the lungs is affected by gravitational settling, Brownian motion, and inertial impact (Fig. 6A) [175]. Liposomes are of various types, and the specific synthesis (Fig. 6C) and drug release mechanisms can be seen in Fig. 6B. Liposomes have been used as carriers of pulmonary drugs, including antibiotics, anti-cancer drugs, enzymes, genes, and anti-asthmatic drugs. For example, concerning antibiotics, liposomal formulations of inhaled drugs are used to maintain drug release, prolong drug action at the infection site, and enhance bactericidal action to maintain antibacterial drugs above the minimum inhibitory concentration in the respiratory tract. Slow release of antibiotics reduces the frequency of drug administration and improves patient compliance [176]. When delivered to the respiratory tract, liposomes are phagocytosed and degraded by macrophages, which release the antibiotics therein [177]. In 2018, the FDA approved inhaled liposomal amikacin for treating Mycobacterium avium complex infections. Liposomal amikacin enhances antibiotic exposure in the lungs compared with intravenous administration [178]. Arikace® is an inhaled liposomal formulation of amikacin, a neutral liposome-encapsulated drug comprising dipalmitoylphosphatidylcholine and cholesterol [179]. Liposomal formulations of ciprofloxacin can be released sustainably [29,180], reducing the frequency of administration and easing treatment [181]. Similarly, polymyxin B liposomes have been produced using the film hydration technique with bis-myristoyl phosphatidylglycerol and surfactants, such as Tween 80 and Span 20. The minimal inhibit concentration (MIC) value against Pseudomonas aeruginosa was much higher (31.3 MICg/L) than that of pure polymyxin B (3.97.8 MICg/L) [182]. However, using liposomes as drug carriers has some disadvantages, such as instability, relatively high cost of generation, and the induction of free radicals. Extracellular vesicles are suitable carriers of inhaled drugs in the lungs. They have similar properties to liposomes (e.g., structure, composition, drug loading, protection capacity, particle size, and pharmaco kinetics and pharmaco dynamics(PKPD), among others); however, they have limitations such as the inability to be mass-produced and a high cost. Hybrid vesicles synthesized from liposomes and extracellular vesicles have been developed as potential new delivery vehicles for pulmonary inhalation drug delivery [183].

Table 3
Parameters for the design of effective inhalation devices.

	Aerosol properties	Particle properties	Physicochemical properties	Airway and lung properties
Parameters	1) Mass median aerodynamic diameter 2) Geometric standard deviation 3) Fine particle fraction 4) Air/particle velocity	1) Volume diameter 2) Bulk density 3) Tap density 4) Shape 5) Charge	1) Solubility 2) Hygroscopicity	1) Airway structure and diameter of airways 2) Influence of disease state on airway structure 4) Breathing pattern – mouth or nasal breathing

4.1.2. NPs

NPs are used as carriers for pulmonary drug delivery and mucosal vaccination [185]. Due to their improved mucosal adhesion and pulmonary retention properties, they can better control the timing of drug release, significantly inhibit pulmonary clearance, and potentially target cells. Using NPs for pulmonary drug delivery can significantly reduce the frequency of administration, improve patient compliance, and simultaneously allow the targeted delivery of drugs. NPs for effective drug delivery contain three primary components: surface modifiers, therapeutic payloads, and core materials. Hydrophobic or hydrophilic therapeutic compounds can be loaded into nano-drug carriers. Therefore, an appropriate carrier material should be carefully selected for each therapy [186]. Polymers are natural or synthetic macromolecular compounds comprising many small homogeneous constituent molecules. NPs formed using polymers as carriers and loaded with drugs can be used for diagnostic and therapeutic purposes and provide different insertable reagents on the polymer surface or dispersed in the polymer [187]. Combining inhalation therapies with nanomedicines has great

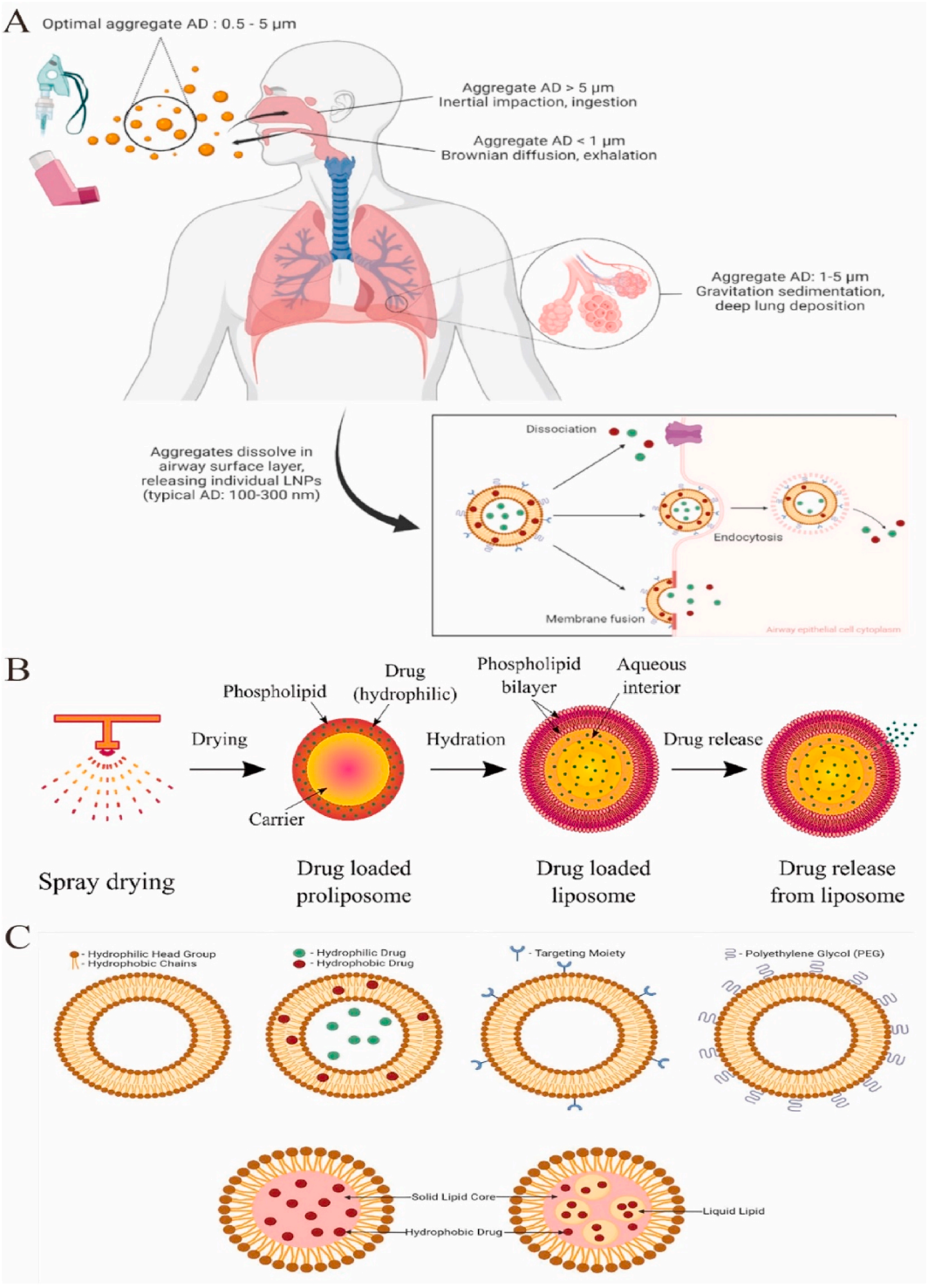

Fig. 6. Liposomal drug delivery systems for pulmonary drug delivery (A) Schematic representation of the distribution and deposition mechanisms of inhaled liposomes in the airways and lungs, including inertial impaction, Brownian diffusion, and gravitational deposition. Adapted reprinted with permission from Ref. [175], based on CC BY License. (B) Schematic representation of liposome synthesis and drug release mechanisms. Adapted reprinted with permission from Ref. [184] (License number: 1423950-1). (C) A visual representation of the structure and composition of different types of liposomes. Adapted reprinted with permission from Ref. [175], based on CC BY License.

potential for treating and improving the prognosis of systemic and chronic lung disorders. Despite the potential of nanomedicines in lung therapy, safety concerns should be considered when using nanomaterials in therapeutic settings. For example, inhaled NPs can adsorb various pulmonary surfactants, which may compromise their physiological function or change their fate [188]. As NPs encourage macrophage activation, which increases the expression of tumor growth factor-beta, a crucial element in the development of fibrosis, lung fibrosis is a concern [35]. In addition, studies have reported that inhaled NPs may be associated with metastasis in certain cancers [36]. The frequency of use, dose, and properties of the NPs may be related to their safety [189–191]. P-glycoprotein (P-gp) may affect the distribution and

absorption of inhaled drugs, leading to adverse effects [192]. In addition to P-gp, another extrapulmonary efflux protein (breast cancer drug-resistance protein) may be essential for the efficacy and safety of inhaled drugs [193]. These studies may serve as future directions for addressing NP safety.

4.1.2.1. Properties of NPs. NP inhaled, diffused, and deposited in the respiratory tract have properties that differ from those of other particles. NP characteristics include size, charge, hydrophilicity, and hydrophobicity [194] Inhaled NPs are deposited in the pulmonary airways primarily by diffusion through Brownian motion [195]. The interaction of NPs with the respiratory mucosa and macrophage clearance affects drug bioavailability. Lung mucus rapidly penetrates 100–200 nm polyethylene glycol-coated particles 15–35 times faster than uncoated particles [196]. The surface charge of NPs is associated with the clearance of respiratory cilia. The elimination rate constant of chitosan-modified poly(lactic-*co*-glycolic acid) (PLGA) nanospheres is approximately one-third that of unmodified nanospheres, enhancing and prolonging drug action [197]. A schematic of the nanospheres is shown in Fig. 7B. Hydrophilic NPs outperform hydrophobic regarding mucus penetration and have a higher deposition rate [198]. The hydrophobic drug carboxy-butylated methotrexate replaced 50 % of the surface PEG moieties. Mucus cilia clearance was twice as high as that of the full polyethylene glycolated poly(lysine) dendrimers [199]. However, the phagocytic behavior of AM reportedly depends on particle size, surface charge, and surface modification [198]. Surface ligand modification and stiffness tuning of NPs significantly enhance the bronchial mucosal uptake and lung retention of inhaled drugs [200]. Therefore, although NP properties make them promising carriers for inhaled drugs, further studies are needed to determine the appropriate range of these properties better to understand their role as pulmonary drug delivery carriers.

4.1.2.2. Lipid-based NPs. Lipid nanoparticles (LNPs) are lipid vesicles with a homogeneous lipid core comprising therapeutic agents placed within a lipid coating [201,202]. The least harmful nanocarrier classes, LNPs, are small artificial spherical complexes based on lipids compatible with human physiology [203,204]. LNPs are currently considered nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) [202]. The diameter of NLC is typically between 100 and 500 nm, whereas that of SLN is between 50 and 1000 nm [205,206]. Lipid coatings have been suggested to help NPs undergo cellular uptake, penetrate the lung barrier, and overcome clearance mechanisms, increasing the retention time of inhaled drugs in the airways [207,208]. LNPs have been demonstrated to deliver nucleic acids, protein/peptide therapies, small-molecule medicines, and drugs cytotoxic against target cells deep into the lung tissue [209–211]. Encapsulation within LNPs can improve drug retention time. In dialysis membrane experiments where solvent oxyfloxacin concentrations were measured at intervals, SLN-oxifloxacin had 24-h sustained release characteristics [30]. Drug solubility and bioavailability are increased by encapsulating hydrophobic drugs in LNPs, particularly SLN, and NLC [204,212]. Recent studies in rats and mice further supported using LNP for delivering chemotherapeutic agents to lung tumors. Encapsulated paclitaxel, rapamycin lactone, and silymarin in SLN administered differently to rats

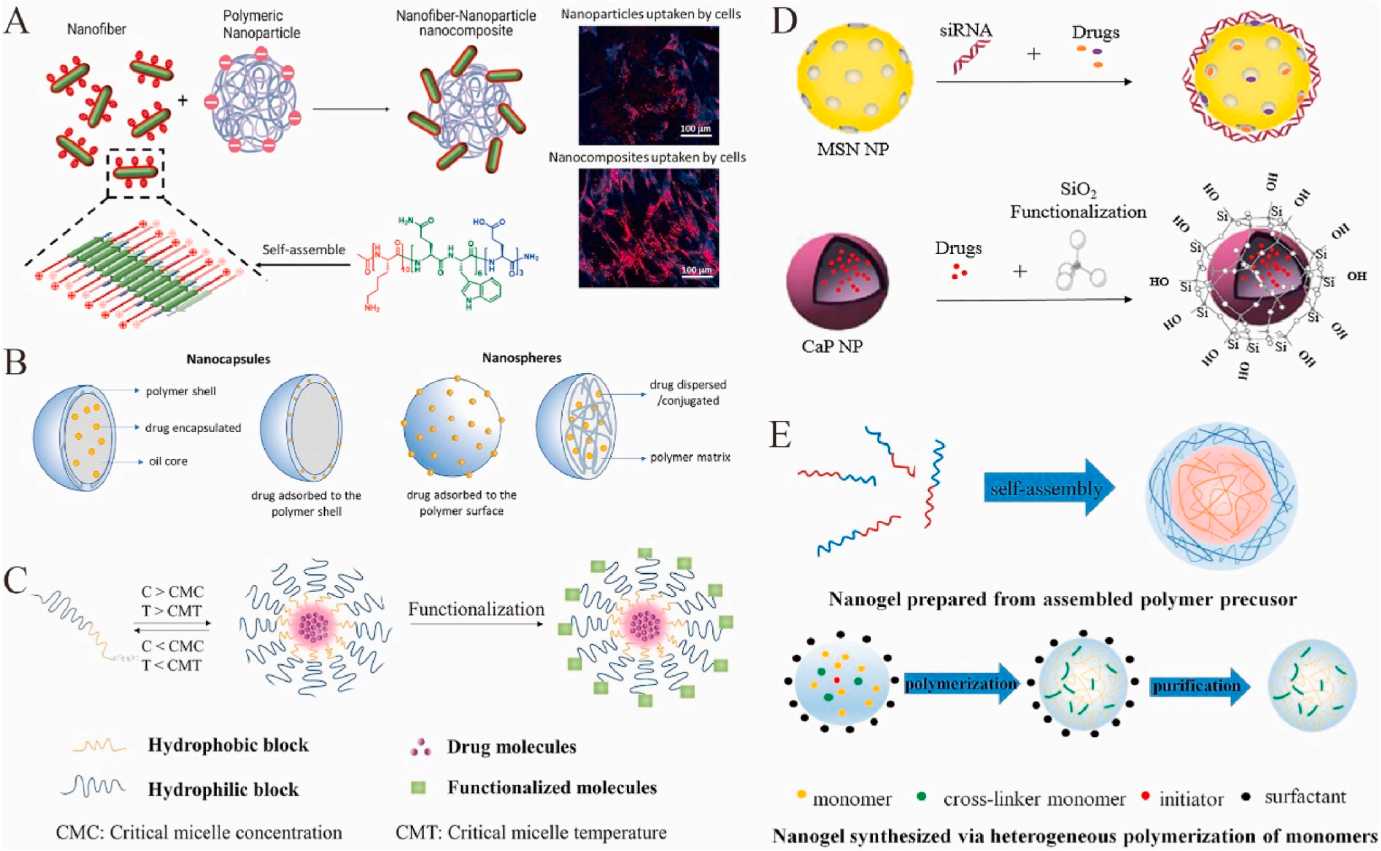

Fig. 7. Inhaled nanodrug delivery system for pulmonary drug delivery (A) Schematic illustration of the synthesis of a novel polylactic-glycolic acid nanocomposite with confocal images showing enhanced uptake of this nanocomposite by primary alveolar type I epithelial cells. Adapted reprinted with permission from Ref. [228]. Copyright © 2022 American Chemical Society. (B) Schematic illustration of the Synthesis of Nanospheres and Nanocapsules. Adapted reprinted with permission from Ref. [184](License number: 1423950-1). (C) Mechanism of polymer micelle formation. Adapted reprinted with permission from Ref. [254](License number: 5,681,951,318,156). (D) Structure of inorganic NPs. Adapted reprinted with permission from Ref. [184](License number: 1423950-1). (E) The two methods for the synthesis of nanomicrogel spheres. Adapted reprinted with permission from Ref. [255] (License number: 5,684,270,099,206).

showed that they exhibited higher drug bioavailability and anti-cancer efficacy in the lungs than bare or intravenously administered LNP formulations [213–215]. Recent preclinical studies have shown that LNPs can locally deliver various medications, including chemotherapeutic agents, antibiotics, mucolytics, vasodilators, mRNA, and siRNAs to the lungs for treating lung diseases such as microbial infections, obstructive lung disease, and lung cancer [175]. Although LNPs are among sophisticated drug delivery technologies, research on protein and peptide medication payloads compared with those of small molecules and nucleic acid remains lacking [216–218]. The development of inhaled LNP drugs remains in its early stages; however, they have great potential for treating various lung diseases and some systemic diseases.

4.1.2.3. Polymeric NPs with targeting groups. Targeting the lungs can be achieved by attaching a targeting ligand or an antibody that does not harm other cells to the polymeric NPs. Many lung-targeting ligands for NP delivery systems exist, including peptides and glycans. With targeted delivery, the therapeutic substance can be delivered to the target site at the same concentration and a lower dose, reducing the likelihood of non-specific harmful effects [186]. To enhance the anti-tumor efficacy of drugs, NPs with an active targeting fraction are usually designed to interact with lung tumors, such as folate receptors, luteinizing hormone-releasing hormone receptors, metalloproteinases, and epithelial growth factor receptors [219–222]. To target membrane markers expressed by macrophages, such as tumor necrosis factor and CD86, NPs can be modified using antibodies or peptides [223]. Endothelial cell adhesion molecules such as E-selectin, vascular cell adhesion molecule-1, and intercellular cell adhesion molecule-1 can be targeted [224,225]. Specific functional peptides can be modified into NPs with or without cage-like structures and desirable nano-properties regarding size and geometry [226].Protein nanocarriers are biodegradable, highly biocompatible, have controlled release properties, modifiable and targeted [227]. Poly(lactic acid glycolic acid) (PLGA) NPs were coated with cell-penetrating peptides (CPP), showing a three-fold higher intracellular delivery of NPs in various cells compared with bare PLGA NPs, a ten-fold increase in endothelial cells, and a two-fold increase compared with conventional monomeric CPP-modified NPs (Fig. 7A) [228].

Similarly, the lectins expressed on the surface of airway epithelial cells can be targeted by sugar-based NPs [229]. Using baculovirus vectors and virus-like particles conjugated to human respiratory syncytial virus fusion proteins to construct protein nanovector vaccines and inoculation-induced distinct innate and adaptive cell subpopulations may prevent lung disease following human respiratory syncytial virus infection [230,231].

4.1.2.4. Micelles. Polymer micelles are another type of polymer nanocarrier. Micelles are thermodynamically stable colloidal agglomerates with ordered arrangements of molecular self-assemblies. The formation mechanism is that after the surfactant with an adsorption capacity reaches saturation, the excess is dispersed in the aqueous solution. Because of the hydrophobic groups, the repulsive force between water molecules and surfactant is stronger than the attractive force, causing the hydrophobic groups to bond through van der Waals forces and form the core of micelles(Fig. 7C). The hydrophilic groups are to be directed outward to form the outer layer of the micelles. Polymer micelles can be prepared via direct dissolution, oil-in-water emulsification, film hydration/solvent volatilization, dialysis, or freeze-drying [232]. The characteristics of the micelles are as follows: 1) small particle size in the range of 10–100 nm; 2) highly stable structures owing to the conjugation of low-molecular-weight surfactants; 3) good solubility; 4) low toxicity; 5) the presence of a lipophilic core and a hydrophilic shell, making the micelles multifunctional. These micelle characteristics make them suitable carriers for pulmonary drug delivery. Through *in vivo* and *in vitro* experiments, Pellosi et al. [233] demonstrated the potential of Pluronic® hybrid micelles for the pulmonary delivery of weakly water-soluble medicines. Anhydrous counter micelles were created by Huang et al. [234] to combat the settling instability of pressurized MDI-containing peptides. Furthermore, Previous studies have evaluated the potential of using poly(ethylene oxide)-*block*-distearoyl phosphatidylethanolamine polymers to prepare micelle carriers and the surface potential of polymeric micelles regarding encapsulation efficiency, slow-release behavior, and biocompatibility as a multifunctional delivery system for treating chronic lung disease [235]. Targeted drug delivery is an advantage of polymeric micelles over conventional pulmonary drug delivery carriers. Zhang et al. [236] designed and constructed a versatile lung-targeting NP. The self-assembled micelles were based on their specific amphiphilic structure and comprised the duckweed seed secondary saponin element 3-*O*-β-D-glucopyranosyl lentil element 682 (GP-682). The particle size of the GP-682 micelles ranged from 60 to 90 nm, which significantly enhanced cell membrane permeability and improved *in vitro* drug uptake. Moreover, it reduced lung injury, bacterial invasion, and cytokine expression compared with treatment with levofloxacin alone. However, a few polymeric micellar formulations are currently available in the market, and many products remain in clinical studies and require further research.

4.1.2.5. Inorganic NPs. Inorganic NP carriers are another NP carrier type for drug delivery in the lungs. Inorganic NPs have been created using various inorganic materials, including dioxide, silicon, gold, iron oxides, titanium dioxide, and alumina. Inorganic NP carriers are highly biocompatible, efficient, stable, magnetic, and anti-microbial [237]. Inorganic NPs are shown schematically in Fig. 7D. Several studies have described the anti-microbial properties of inorganic NPs against pulmonary infections [238,239]. Dames et al. [240] used aerosol droplets containing superparamagnetic iron-oxide NPs (also known as nanomagnetosols) in conjunction with a target-directed magnetic gradient field. They contended that nanomagnetosols could cure local lung ailments by concentrating on bacterial infection foci or tumor nodules. The cyclodextrin-based organic backbone has a homogeneous nanoporous structure, exhibits excellent nebulization properties, and good biocompatibility, does not affect lung function, and does not induce inflammatory responses [241]. Due to their wide pores, large surface area, and capacity to load significant amounts of pharmaceuticals, MSNs have been investigated as alternative technology platforms for pulmonary drug delivery [242]. A novel class of nanomedicines for treating inflammatory lung diseases, such as acute respiratory distress syndrome (ARDS), infections, and COPD, can be created using passive targeting of MSN, which has been documented for targeting inflamed tissues and tumors [243]. Therefore, MSNs are suitable carriers for pulmonary drugs [244]. In addition, MSNs have effectively managed lung cancer [245]. One study reported a highly versatile nanoplatform that combines MSN with aerosol technology to enable direct nanoscale delivery to the respiratory tract. This delivery method was successfully tested in mice via inhalation [246]. Safety is a crucial factor in drug delivery vehicles. Using inorganic NPs (silica, titanium dioxide, and graphene) in animals reportedly shows significant inflammatory responses [247]. Although inorganic NPs have been extensively studied, further research is required for their clinical application.

4.1.2.6. Hydrogel nanospheres. Microhydrogels are appealing pulmonary drug delivery carriers and can be created to be delivered to the bronchi and to expand upon arrival, preventing absorption and clearance by AM. Additionally, for effective lung deposition, microhydrogels can be created with particles of size 0.5–5 μm [248]. Secret et al. [248] created spherical polyethylene glycol diacrylate particles by incorporating peptides into polymer chains from a high-molecular-weight polyethylene glycol diacrylate-based precursor. These particles are enzyme-responsive hydrogel microparticles for inhalation delivery to the lungs. In a follow-up study, the viability of these hydrogel particles as protein (horseradish peroxidase), hydrophilic (methylene blue), and

hydrophobic (dexamethasone) drug carriers was demonstrated; it was non-toxic [249]. Similarly, the feasibility of using hyaluronic acid hydrogels to design inhalation powders for controlled pulmonary drug delivery has been evaluated, and a combination of chemical crosslinking and spray drying has been proposed as a new method for preparing inhalation powders [250]. The steps of the two methods of synthesizing nanomicrogel spheres are shown in Fig. 7E. Nexinhib20 is a potent inhibitor of neutrophil degranulation. Constructing a self-regulating microgel NP system where NPs are loaded with Nexinhib20 and extracellular elastase (degranulation by inflammatory neutrophils) reportedly induces microgel activation. After a successful delivery to neutrophils *in vivo*, nexinhib20 encourages remission of the inflammatory response [251]. Shahin et al. [252] prepared spray-dried hydrogels containing various concentrations of biodegradable sodium carboxymethylcellulose, sodium alginate, and sodium hyaluronate polymer microparticles that showed good results *in vivo* and *in vitro* for the pulmonary administration of sildenafil citrate. In addition, nanomicrohydrogel particles loaded with ciprofloxacin-controlled drug release and prolonged lung drug concentration after delivery to rats using intratracheal blowing [253]. These studies suggest that hydrogel particles are potential carriers in pulmonary drug delivery and have great advantages regarding slow drug release and prolonged pulmonary drug concentrations, which require further exploration.

4.2. Gene delivery system for pulmonary drug delivery

In pulmonary drug delivery systems, delivering conventional and specific drug types, such as genes, is essential. Genes alone are relatively safe in the body and cause no toxicity or immune disorders; however, they cannot be delivered effectively owing to the presence of various enzymes. Since nuclease activity is lower in the surface environment of the lung than in the serum, inhalation delivery reduces the drug dose and potential systemic adverse effects and facilitates maintaining RNA stability. A recent study described the screening and characterization of a polymeric NP, P76 (a poly-β-amino-thioester polymer), capable of delivering various mRNAs to the lungs of different animals, including mice, hamsters, ferrets, cows, and rhesus monkeys, using with a highly safe and tolerable nebulized inhalation [256]. Another study involved constructing an inhaled mRNA nanoformulation for delivering matrix metalloproteinase-13 mRNA and keratinocyte growth factor and showed that inhaled delivery effectively reduced the level of lung tissue fibrosis in mice, synergistically restoring alveolar integrity and improving lung function (Fig. 8A) [257]. Dopamine (DA)-grafted hyaluronic acid, synthesized by electrostatic attraction and easily encapsulated in poly(-amino ester) (BP)-based siRNA carriers, showed significantly enhanced mucus penetration [258]. Inhalable polymeric NP formulations with mRNA payloads and poly(-amino ester) libraries have been reported to safely and successfully deliver therapeutic mRNA molecules to the lungs of various animals [259]. Screening synthetic LNP libraries *in vivo*, researchers discovered that LNPs with tail structures, including amide bonds, could precisely deliver mRNA to the mouse lungs. Moreover, changing the head structure of LNPs enabled the targeting of different lung subcell types [260]. However, even in the most clinically advanced delivery systems, LNPs suffer from inefficient intranuclear body escape [69]. Xu et al. [261] designed a DPI formulation of LPN loaded with siRNAs, targeting the nebulization of inhalation therapy. The RCB-4-8 LNP was identified as capable of constructing inhalable delivery vectors for the CRISPR-Cas9 gene and editor messenger RNA [262]. Exosomes are ideal delivery options for inhaled mRNA. One report indicated that exosomes could be employed as inhalable mRNA drug carriers and are more suitable than LNPs for delivering inhalable mRNA medications; however, marketed products are unavailable (Fig. 8B) [263].

5. Application of pulmonary drug delivery

Lung diseases (including lung cancer, COPD, and asthma) are the third leading cause of death worldwide and are treated differently. Notably, pulmonary drug delivery is a fast route of administration for different diseases and conditions of the lungs [264] and has a high concentration of lung-targeted drug delivery, a lower drug dose that avoids gastrointestinal absorption and portal circulation, a faster onset of action, and reduced side effects. It is a non-invasive modality for patients with less pain and better compliance. In this section, we describe the applications and recent progress in pulmonary drug delivery for each of the lung diseases. Furthermore, we expanded the use of pulmonary drugs for some systemic diseases.

5.1. Use and progress of pulmonary drug delivery in neo-crown pneumonia

COVID-19 is a novel coronavirus that causes severe acute respiratory syndrome. Studies have shown that healthy lung tissue alveolar epithelial cells highly express angiotensin-converting enzyme receptor 2 (ACE2) [265]. ACE2 facilitates the entry of SARS-CoV-2 into the cells [266]. Thus, in COVID-19-induced respiratory disease, the lungs are the primary infected and damaged organs. The accumulation of cytokines, chemokines, and reactive oxygen-rich fluid disrupts intact alveolar structure and function, causing low blood oxygenation levels (Fig. 9A) [267]. Pulmonary inhalation is a promising treatment option for this disease owing to its efficacy and safety. It is believed that hydroxychloroquine (HCQ) and chloroquine (CQ) impede viral terminal glycosylation of ACE2; however, they do not alter ACE2 in mammalian cells; therefore, they might theoretically be used to treat neo-crown pneumonia [268]. Studies have shown that HCQ inhalation is safe and effectively tolerated [269]. *In vitro*, inhalation of CQ or HCQ may produce therapeutically effective lung concentrations [270]. HCQ can be formulated as an inhalable dry powder by jet-grinding HCQ sulfate [271]. Li et al. [272] developed an ACE2 receptor-binding domain that can inhibit SARS-CoV-2 infection and found that adding gelatin significantly stabilized the protein and increased the active protein fraction after aerosolization, minimizing the drug dose. A formulation of favipiravir SLN was prepared for pulmonary delivery using the thermal evaporation method [273]. The fact that the lung tissue immediately produces an effective medication concentration is the greatest benefit of inhalation therapy. Within 7 days, rats exposed to nebulized inhaled ivermectin showed detectable lung levels [274]. IIslam proposed a new strategy for pulmonary drug delivery of the antiviral drug amantadine and suggested that it might be a more effective approach for treating patients with Parkinson's disease and COVID-19-related complications and a more effective strategy [275]. Additionally, reports recommend a combination of broad-spectrum antiviral drugs for treating neo-coronary pneumonia, and the development of nanomedicines is anticipated (Fig. 9B) [267]. Xuan et al. [276] reported an inhaled bioadhesive hydrogel-based physical barrier, called spherical hydrogel inhalation (SHIELD), targeting the SARS-CoV-2 infection barrier. SHIELD particles are conveniently delivered via a dry powder inhaler, forming a dense hydrogel network covering the airway, enhancing the diffusion barrier properties, and limiting viral penetration (Fig. 9C). Thymoquinone has broad-spectrum antibacterial, antioxidant, and anti-inflammatory effects, suggesting its potential use in secondary infections caused by COVID-19 [277]. With the advantages of safety, restoration of oxygenation, downregulation of cellular inflammatory factors, and re-establishment of immune system function, exosomes are promising candidates for treating neo-crown pneumonia. Mesenchymal stem cell-derived exosome nebulizer therapy promotes the resorption of lung lesions [278]. These studies provide insights into the effective prevention and treatment of neo-coronary pneumonia.

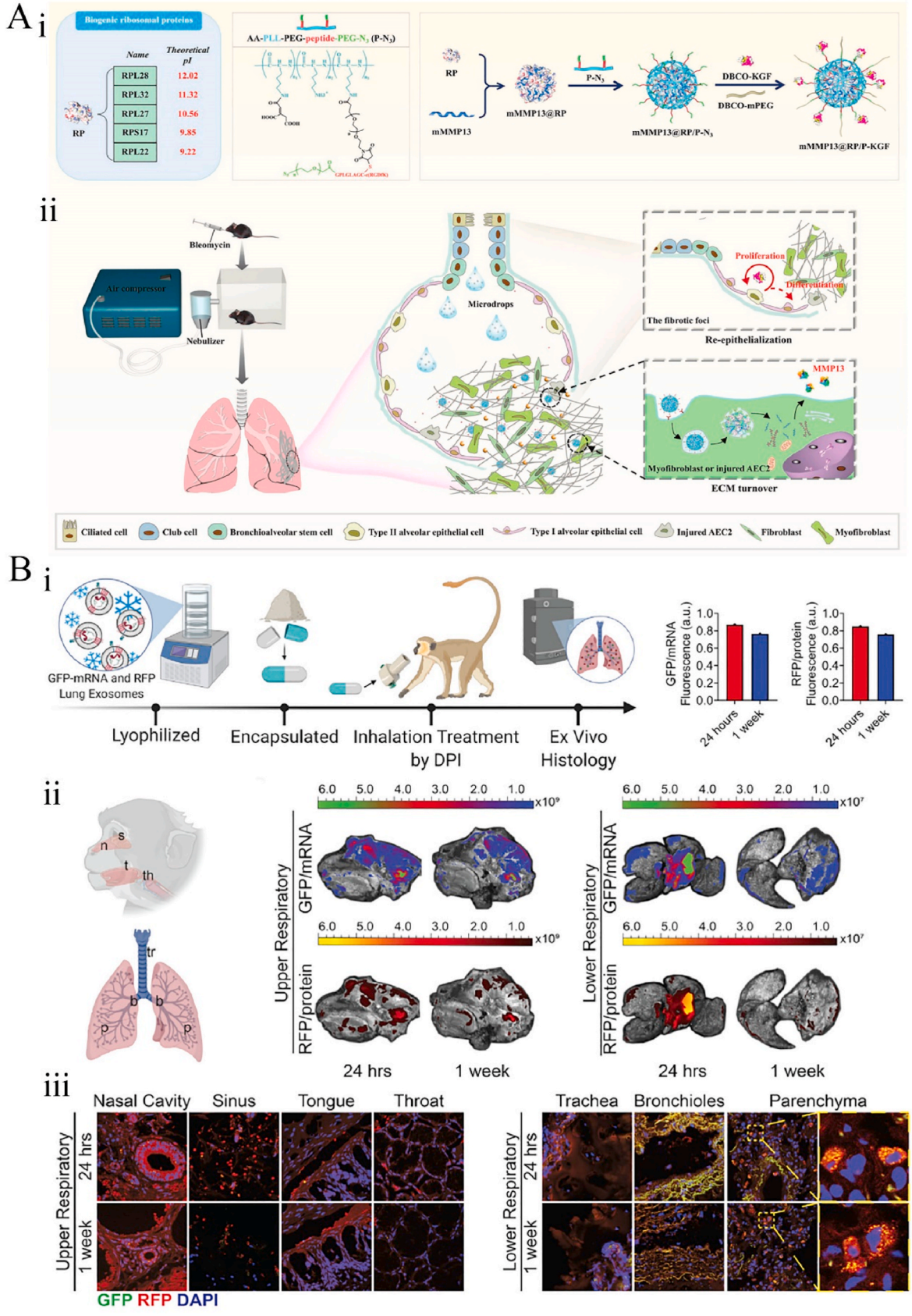

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Fig. 8. Gene delivery systems for pulmonary drug delivery (A) Schematic representation of inhaled messenger ribonucleic acid nanoformulations prepared from biological ribosomal proteins for the reversal of established idiopathic pulmonary fibrosis (i) A class of biologically derived ribosomal proteins with multiple isoelectric points, as well as a matrix metalloproteinase reaction and inhaled mRNA nanoformulation (defined as mMMP13@RP/P-KGF), was constructed. (ii) Therapeutic mechanisms of mMMP13@RP/P-KGF. Adapted reprinted with permission from Ref. [257](License number: 5,681,961,163,234). (B) Inhalation of mRNA- and protein-carrying dry powder reagents by African green monkeys. i) Synthesis of mRNA- and protein-carrying DPIs and schematic *in vitro* lung histology after inhalation by a primate Quantification of GFP and RFP fluorescence integral densities in primate lungs (ii) Schematic illustration of histological sections and *in vitro* images of the upper respiratory tract (including the nasal cavity (n), sinuses (s), tongue (t), and larynx (th)) and the lower respiratory tract (including the trachea (tr), bronchi (b), and lungs (p)). (iii) Representative immunostaining images of GFP (green), RFP (red), and DAPI (blue) of the nasal cavity, sinus, tongue, larynx, trachea, fine bronchus, and parenchyma sections. Adapted reprinted with permission from Ref. [263], based on CC BY License. Abbreviations: GFP: Red fluorescent protein. RFP: green fluorescent protein. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

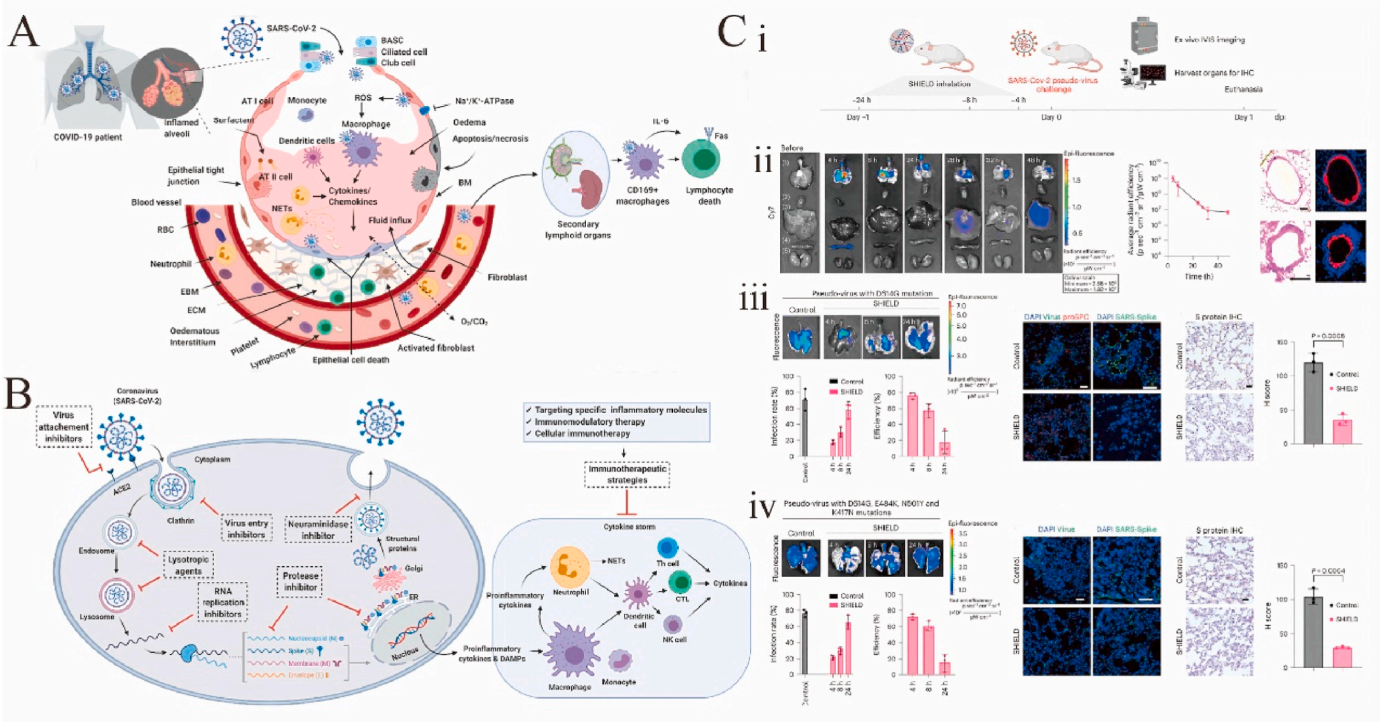

Fig. 9. Pulmonary inhalation drug delivery for the treatment of a new type of coronary pneumonia (A) Lung pathology in COVID-19. Adapted reprinted with permission from Ref. [267] (License number: 5,682,810,691,400). (B) Therapeutic strategies for COVID-19. Adapted reprinted with permission from Ref. [267] (License number: 5,682,810,691,400). (C) SHIELD inhalation protects African green monkeys from SARS-CoV-2 infection. (i) Schematic illustration of the non-human primate study design (ii) Analysis of viral load in nasal swabs and alveolar lavage fluid and representative H&E images of lung tissue from SARS-CoV2-infected African green monkeys (iii) Representative images of SARS-N IHC staining, quantification of the number of SARS-N positives, and RNA scope in situ hybridization for detection of infected vRNAs in fixed lung tissues of monkeys infected with SARS-CoV-2 at 7 days after the viral attack. (iv) Representative immunofluorescence images of CD206 (green), SARS-N (greyscale), and DAPI (blue) for WA1-challenged. Adapted reprinted with permission from Ref. [276](License number: 5,682,820,608,805). Abbreviations: SHIELD: An inhalable bioadhesive hydrogel based on a spherical hydrogel for enhanced lung defense forms a physical barrier against SARS-CoV-2 infection. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

5.2. Pulmonary drug delivery in vaccination

This vaccine can be administered via inhalation to the lungs to induce a mucosal immune response. This local response can improve the efficacy of pathogen immunization [279]. Mucosal vaccines activate the immune response in the mucosa and system of the body to control infectious diseases. Compared with intramuscular vaccines, mucosal vaccines prevent the replication of viruses and bacteria in the upper respiratory tract and block human-to-human transmission. Depending on the immunization type, mucosal vaccines can be divided into intranasal and inhalation types. Nebulized vaccinations administered through the nose or mouth can reach deep inside the lungs. A history of inhalation vaccination of the lungs was recorded since 100 BCE when powdered crusts from patients infected with smallpox were delivered through a small blowpipe into the noses of uninfected patients or dispersed in the air for inhalation [280]. Inhalation vaccines targeting the respiratory tract have recently received considerable attention. Respiratory vaccination formulations should overcome several airway barriers to protect after administration (Fig. 10A) [281]. Bennett et al. reported that the measles vaccine was more immunogenic when administered as an aerosol than when injected [282]. Adjuvants are compounds that must be administered along with the antigen in the formulation to produce an appropriate immune response when used with mucosal immunization antigens [283]. *In vivo*, mild humoral and cytotoxic immune responses were observed after the intrapulmonary injection of cAMP as a mucosal adjuvant [284]. Dry powder reagents are attractive formulations for pulmonary vaccines. Audouy et al. used spray freeze-drying to produce an influenza vaccine for pulmonary vaccination and demonstrated that protection comparable to that of intramuscular immunity could be obtained in mice [285]. Muttil et al. [286] reported an NP immune formulation that showed higher levels of protective antibodies and high local IgA antibody titers after pulmonary administration than after intramuscular administration in guinea pigs in an *in vivo* experiment. Dry powder inhalers of S-protein-loaded lung-derived exosomes induced stronger immune responses (Fig. 10B) [263]. The morphology of the pulmonary inhalation formulations is

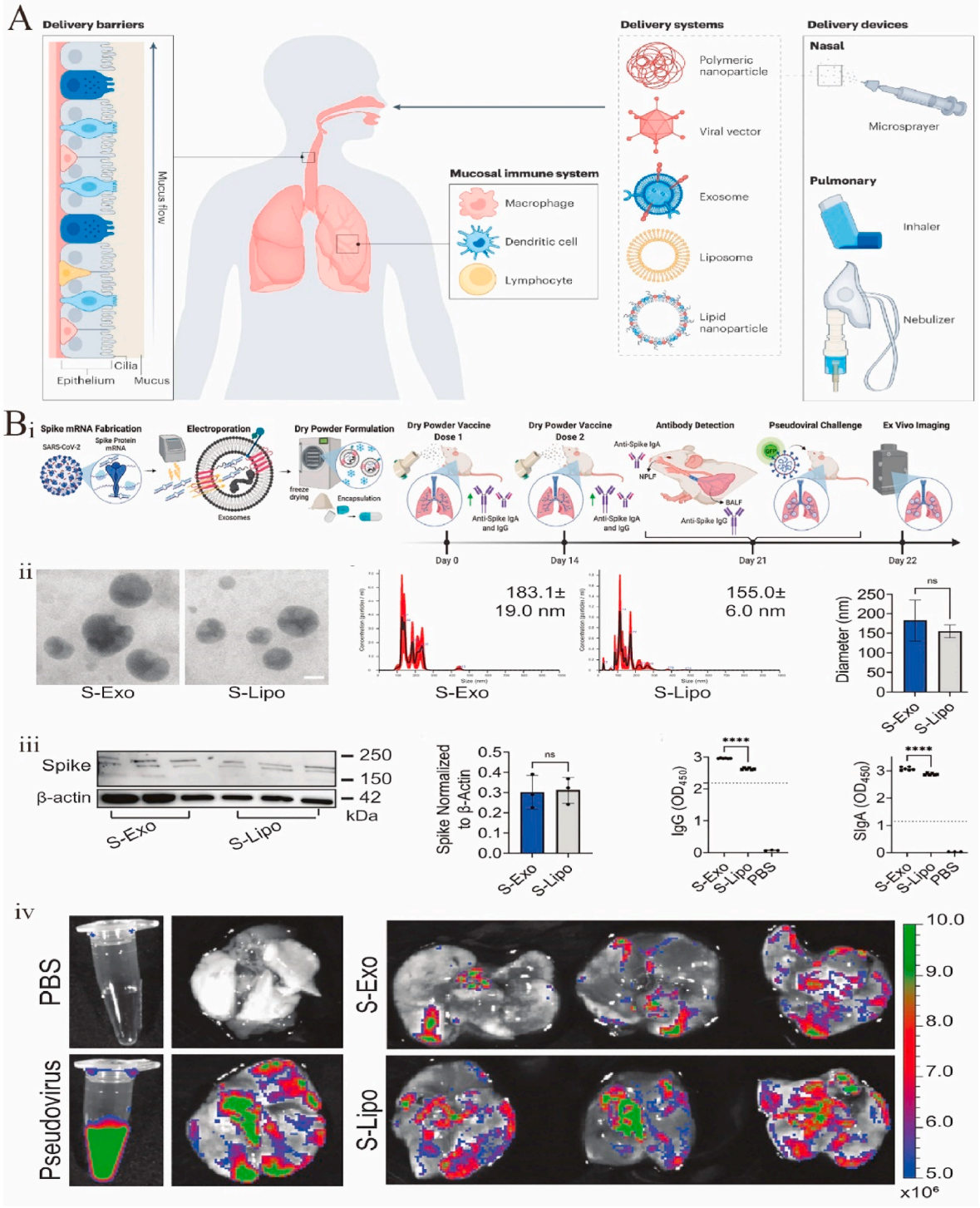

Fig. 10. Pulmonary delivery in vaccination.(A) Schematic illustration of intranasal and pulmonary inhalation vaccine delivery. Adapted reprinted with permission from Ref. [281](License number: 5,682,821,155,144). (B) Dry powder inhalers of S-protein-loaded lung-derived exosomes induced stronger immune responses. (i) Schematic representation of DPI-induced immune response.(ii) TEM images of S-Exos and S-Lipos at room temperature, NTA size distribution analysis, and quantification (iii) Immunoblotting of S-protein in mouse lungs, quantification of β-actin, Anti-Spike IgG antibody titer, and Anti-Spike SIgA antibody titer (iv) Lungs of the ex vivo images before and 24 h after inoculation. Adapted reprinted with permission from Ref. [263], based on CC BY License.

equally significant. Recent studies have shown that vaccines based on nonspherical polymersomes may be more effective than those based on spherical polymersomes, particularly against viruses used for pulmonary drug delivery [287].

Pulmonary inhalation vaccines have recently been an effective method for combating the global COVID-19 pandemic. Inhalation of the nebulized adenovirus type 5 vector COVID-19 vaccine (Ad5-nCoV) in ongoing phases 2 and 3 clinical trials is painless, simple, and tolerable [288]. Furthermore, heterologous booster immunization with nebulized Ad5-nCoV in previously vaccinated adults is safe, highly immunogenic, and causes significantly higher concentrations of serum-neutralizing antibodies than the homologous third dose of CoronaVac [289]. Vaccines administered via the respiratory tract should overcome various barriers in the airways to be effective. Compared with intramuscularly

delivered vaccines, inhaled NP vaccines coated with polyethylene glycol have been demonstrated to rapidly permeate the mucus barrier and boost the proliferation of T lymphocytes in the lungs and lymph nodes [290]. The SARS-CoV-2 receptor binding domain from lung-derived exosomes can be used to create an inhalable vaccine that stimulates a powerful immune response in mouse airways [291]. Several COVID-19 intranasal and inhalation vaccinations are currently undergoing clinical testing [292]. Although great progress has been made in using pulmonary vaccines, intranasal and inhaled vaccines lack suitable animal and further development of models.

5.3. Pulmonary drug delivery in pulmonary infections

Pulmonary infections are usually defined as a substantial inflammation of the lungs, including the terminal airways, alveolar cavity, and interstitium, and are characterized by bacterial infections. Antibiotics are effective treatments for bacterial infections. Intravenous or oral administration is the routine administration mode [293,294]. However, in treating pulmonary infections, oral or intravenous administration suffers from low bioavailability, possible adverse drug reactions, and the development of drug resistance [295–297]. The best strategy to treat lung bacterial infections is with inhalation therapy, which allows medicines to act directly on the lungs [298,299]. Inhaled antibiotic therapy

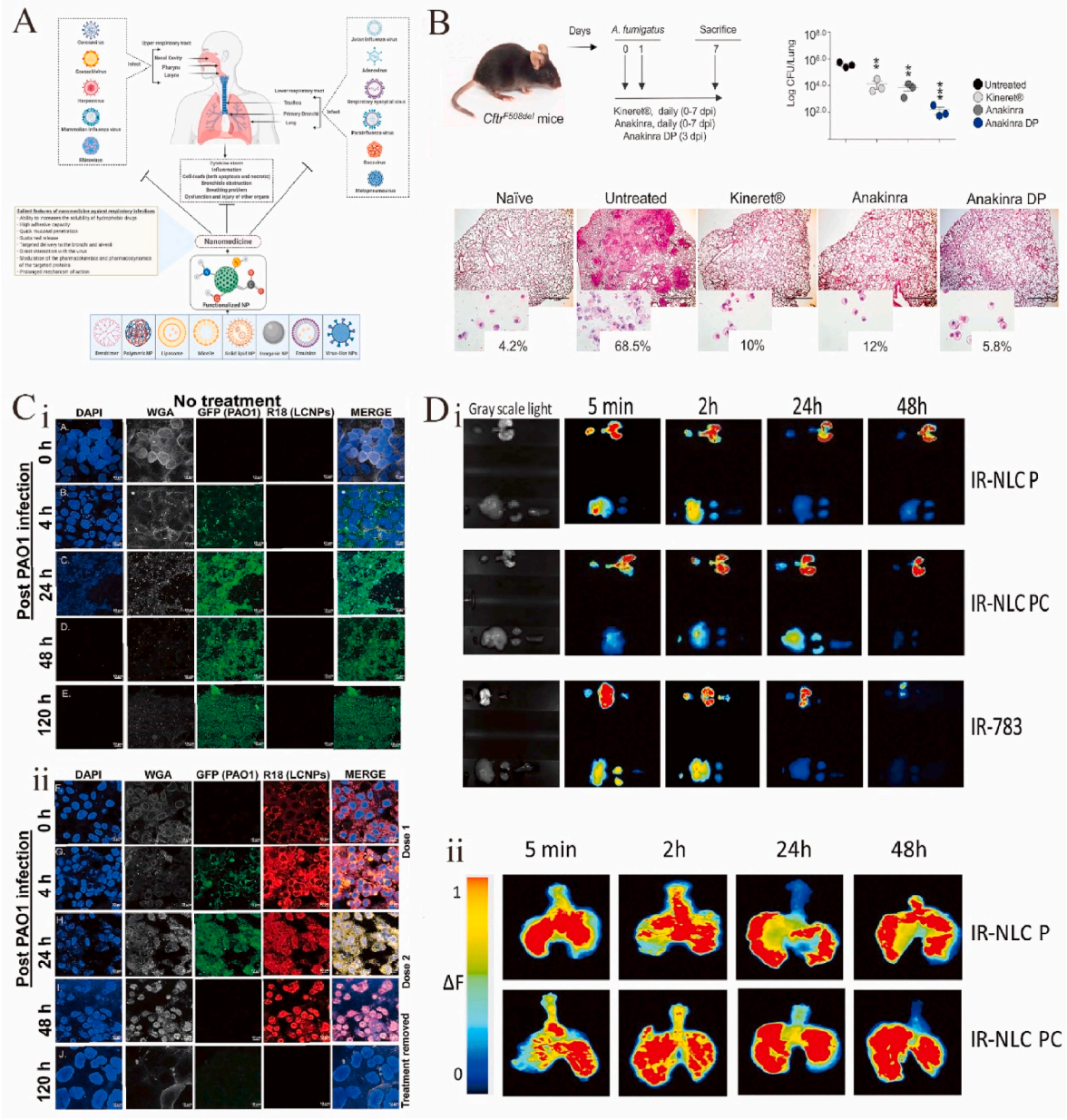

Fig. 11. Pulmonary drug delivery in pulmonary infections (A) Nanomedicine-based strategies to prevent and treat lung infection-related diseases. Adapted reprinted with permission from Ref. [267] (License number: 5,682,830,333,897). (B) Pathological analysis of lung inflammation in cystic fibrosis mice prevented by a single inhalation of Anakinra DP. Adapted reprinted with permission from Ref. [307] (License number: 5,682,830,851,672). (C) Laser confocal scanning microscopy images of (i) untreated PAO1-infected CFBE410 versus and (ii) CFBE410 treated with Tobramycin Monoolein-liquid crystal NPs nebulization. Adapted reprinted with permission from Ref. [308] (License number: 5,682,831,238,758). (D) Biodistribution of (i) IR-NLC and free IR in the heart, trachea, lungs, gallbladder, liver, kidneys, and spleen and (ii) IR-NLC in the lungs after inhalation administration in mice. Adapted reprinted with permission from Ref. [304] (License number: 5,682, 840,135,138). Abbreviations: PAO1:Pseudomonas aeruginosa strain. CFBE41o: cystic fibrosis patient bronchial epithelial cell line. IR-NLCs: NPs labeled with infrared dye.

was employed in the 1940s to treat persistent respiratory infections; however, it produced adverse side effects [300]. Despite decades of development, the amount of inhaled antibiotics remains low. Only four inhaled antibiotics have been approved for clinical use in Europe, namely mucomycin (and its prodrug, mucomycin methanesulfonate), tobramycin, levofloxacin, and aminoglutethimide [301]. Better water solubility, higher drug loading, and appropriate lung deposition and retention times are required for inhaled antibiotic therapy. Appropriate inhaled drug delivery vehicles and devices are promising approaches to address these challenges. The commonly used antibiotic carriers include liposomes [302], microemulsions [303], and lipid NPs [304]. Nanomaterials offer unique advantages for drug delivery in treating infectious lung diseases, including reduced drug toxicity, increased drug solubility, synergistic therapy, and targeted delivery [305]. Nanomedicine-based strategies for the prevention and treatment of lung infection-related diseases are illustrated in Fig. 11A. In addition, the co-delivery of multiple active compounds in a carrier system is a way to improve drug efficiency and prevent drug resistance. Polymyxin B NPs complexed with polystyrene sulfonates of different relative molecular masses showed a 10,000-fold increase in PA inhibition [306]. Matteo et al. [307] successfully developed an inhalable anakinra dry powder to meet the specific requirements of pulmonary drug delivery (Fig. 11B). Thorn et al. [308] fabricated a bionic nanostructured lipid liquid-crystal NP formulation that significantly improved the efficacy of tobramycin and eradicated *P. aeruginosa biofilm infections* (Fig. 11C). Tobramycin-loaded nanostructured lipid carriers are potential alternatives for the treatment of lung infections caused by *P. aeruginosa* (Fig. 11D) [304]. Nevertheless, the variety of inhaled antibiotics for pulmonary infections remains relatively small, and further development of inhaled formulations of other antibiotics is needed to improve their antibacterial efficacy, reduce the required antibiotic dose, and avoid bacterial resistance, which is the future direction for inhaled antibiotic formulations.

5.4. Pulmonary drug delivery in COPD and asthma and progress

Chronic lung disease is usually characterized by bronchial inflammation, airflow limitation, hyperinflammation, and respiratory muscle dysfunction, including emphysema and chronic obstructive bronchitis [264]. Asthma can be considered a type of COPD characterized by episodes of airflow obstruction owing to multiple stimuli, including infections, environmental allergies, and psychological factors. Optimizing bronchodilation is a crucial task in COPD treatment. Combining β-agonists, long-acting bronchodilators, corticosteroids, and anticholinergic drugs is synergistic in treating COPD. Inhaled drug delivery, which can deliver drugs directly deep into the lungs, has advantages (e.g., ease of use, portability, targeted therapy, and few side effects) and has become a highly advantageous mode of drug delivery for COPD and asthma. However, patient compliance has been challenging in treating chronic lung diseases, particularly in older patients, owing to the large variety of drugs used simultaneously, the lengthy treatment time, and the complexity of various pulmonary drug delivery devices. Although a variety of inhalation delivery systems have been developed to treat lung diseases, including Nebs and pMDIs, soft mist inhalers, and DPIs, each device has its advantages, disadvantages, and limitations regarding the type of formulation that can be used, the type of drug that can be administered, and the inhaled dose that can be produced from these devices. Studies have shown that the number of inhalers can affect patient compliance, with higher discontinuation rates when multiple inhalers are used than when a single inhaler is used [309]. Synthesizing multiple formulations into a single formulation in a fixed-dose combination and simplifying the steps of the inhalation device is essential. Nevertheless, the instability of the co-mix suspension and the variability of the administered dose complicate detecting the optimal dose for long-acting β2 agonists (LABA) and long-acting anticholinergics (LAMA) combination therapy [34,310]. Porous particle technology enables the formulation of pMDI combination therapies [86]. One study developed brominated glycopyrronium (glycopyrrolate) in the form of an inhaled MDI, with glycopyrronium as the active ingredient, formulated in special porous particles comprising phosphatidylinositol choline and calcium chloride, a fine-particle formulation that stabilizes the MDI formulation of the drug and delivers the active drug uniformly to the distal airway [311]. Novel inhaled lipid NPs formed from ionizable cationic lipid assemblies deliver siRNA drugs safely and effectively and can potentially alleviate allergic asthma by inhibiting the overexpression of pro-inflammatory cytokines in the airways (Fig. 12) [312]. Polyethylene glycol-distearoyl glycerol-phosphate ethanolamine (PEG-DSPE)-modified polypropylene glycol-co-glycolide (PLGA) microspheres, which can overcome the mucus barrier and macrophage uptake while reducing systemic absorption, should be used for sustained pulmonary delivery [313]. Several formulations are currently available for clinical use, and glibenclamide/formoterol is the first LABA/LAMA fixed-combination therapy available as a pMDI for treating COPD [86]. Since then, several combination therapies have been by the FDA for marketing, including umeclidinium/vilanterol (DPI Ellipta®, Glaxo Smith Kline, Brentford, UK) and tiotropium/olodaterol (Soft Mist Inhaler). On July 24, 2020, a triple combination of budesonide/gelononium bromide/formoterol fumarate MDI, which is more effective than LAMA/LABA in patients with COPD, was approved by the FDA for marketing. Patients with COPD show more significant efficacy [314]. PMDIs are reportedly the most used mode of treatment for COPD [86].

5.5. Application and progress of pulmonary drug delivery in lung tumors

Lung cancer is a common type of cancer and the second most common cause of cancer-related deaths [315,316]. Systemic chemotherapy, a common treatment for lung cancer, is usually administered throughout the body with no specific lung distribution; therefore, severe side effects are inevitable [243]. The inability of chemotherapy drugs to penetrate tumors or the low distribution of drugs in tumor cells after systemic administration is reportedly responsible for the efficacy of chemotherapy drugs [317]. Therefore, local and continuous pulmonary administration with the delivery of the desired concentration of the drug to the tumor tissue while avoiding the deposition of high doses of the drug in other organs is essential to improve the efficacy of chemotherapy. Chemotherapeutic agents and molecularly targeted medications are believed to work better when delivered to the lungs via the respiratory route with fewer systemic side effects. According to one study, highly porous PLGA microspheres containing Adriamycin have greater potential than free administration as long-term extended-release inhalation agents for treating lung cancer and may significantly reduce the cardiotoxicity associated with Adriamycin [318]. Zhu et al. prepared inhalable PLGA oridone porous microspheres for treating in situ lung cancer in experimental rats [319]. He et al. [320]have developed pH-sensitive charge conversion M-HHG2C18-L to co-deliver the synergistic erlotinib/doxorubicin (DOX) combination for lung cancer therapy, which the authors considered to be a highly efficient and promising co-delivery system for cancer chemotherapy (Fig. 13C). The primary dose-related side effects of inhaled drugs include damage to the respiratory tract, including loss of lung function, dyspnea, hoarseness, fatigue, nausea, vomiting, and, less frequently, systemic adverse reactions. Taratula et al. [321] constructed multifunctional lipid NPs modified using polyethylene glycol and luteinizing hormone-releasing analogs. After administration through the lung, the NPs mostly aggregated in the tumor tissue, avoiding normal lung tissue and showing better anti-cancer effects than the control NPs. Immunotherapy is a modality for treating lung cancer, and vital breakthroughs in immune checkpoint blockade (ICB) are currently available. However, ICB immune aerosol therapy for lung metastases remains unachieved. One study designed a unique ICB antibody aerosol inhalation delivery system and demonstrated that repeated inhalation of chitosan/anti-programmed cell death protein ligand 1 complex could effectively activate the immune system, ultimately extending survival to 60 days in mice, which is expectedly

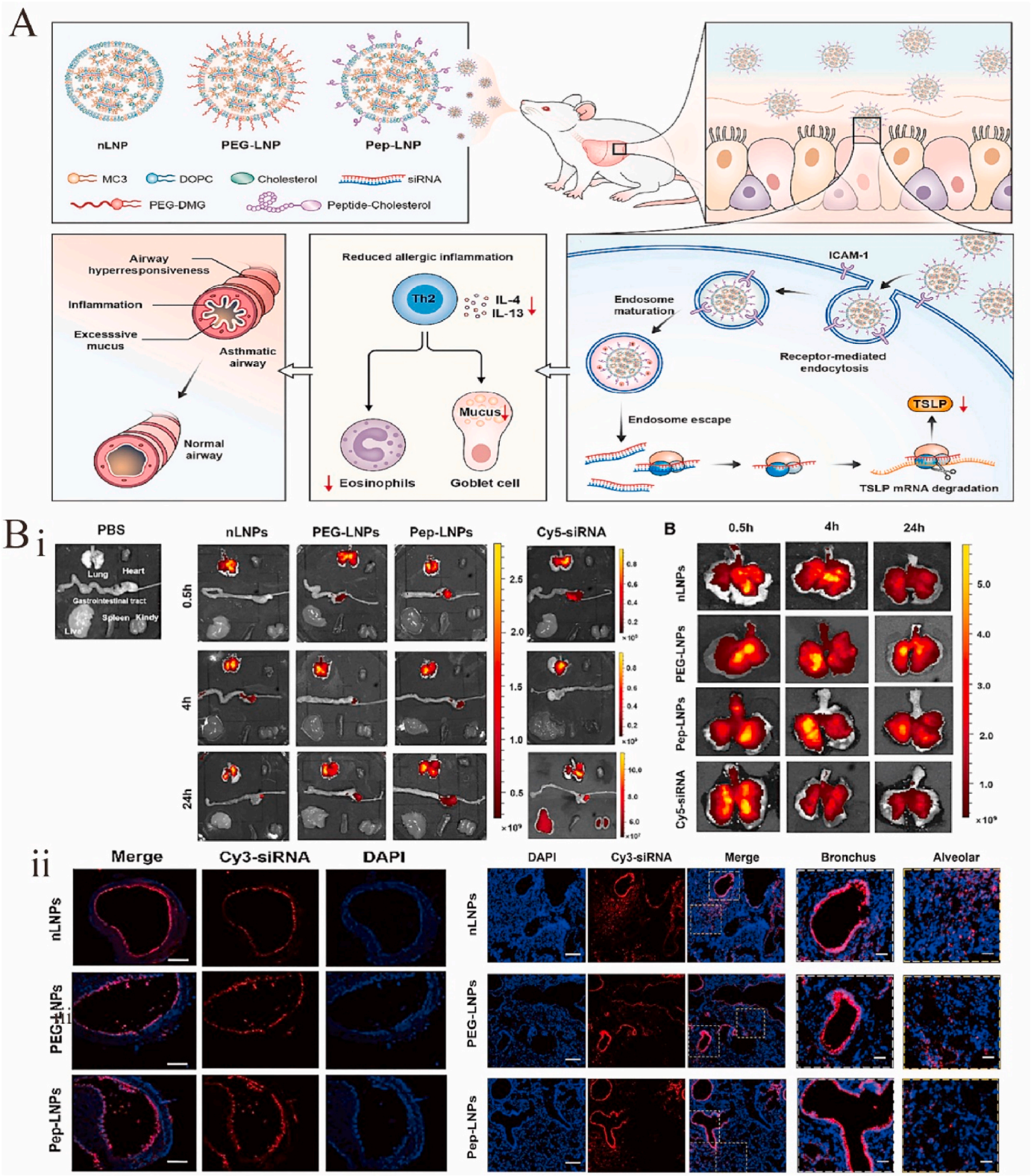

Fig. 12. Pulmonary drug delivery in COPD and asthma.(A) Schematic diagram of LNPs-siTSLP airway epithelial cells specific delivery by pulmonary administration for relief of allergic asthma. Adapted reprinted with permission from Ref. [312] (License number: 5,682,860,146,067). (B) Biodistribution of mouse lungs and various other organs at different time points following pulmonary administration. (i) Typical IVIS images of the biodistribution of mouse lungs and various other organs at different time points. (ii) Average fluorescence intensity of bronchial and alveolar Cy3-siRNA. Adapted reprinted with permission from Ref. [312] (License number: 5,682,860,146,067). Abbreviations: LNPs-siTSLP: novel inhaled LNPscarrying siRNAs targeting thymic stromal lymphopoietin.

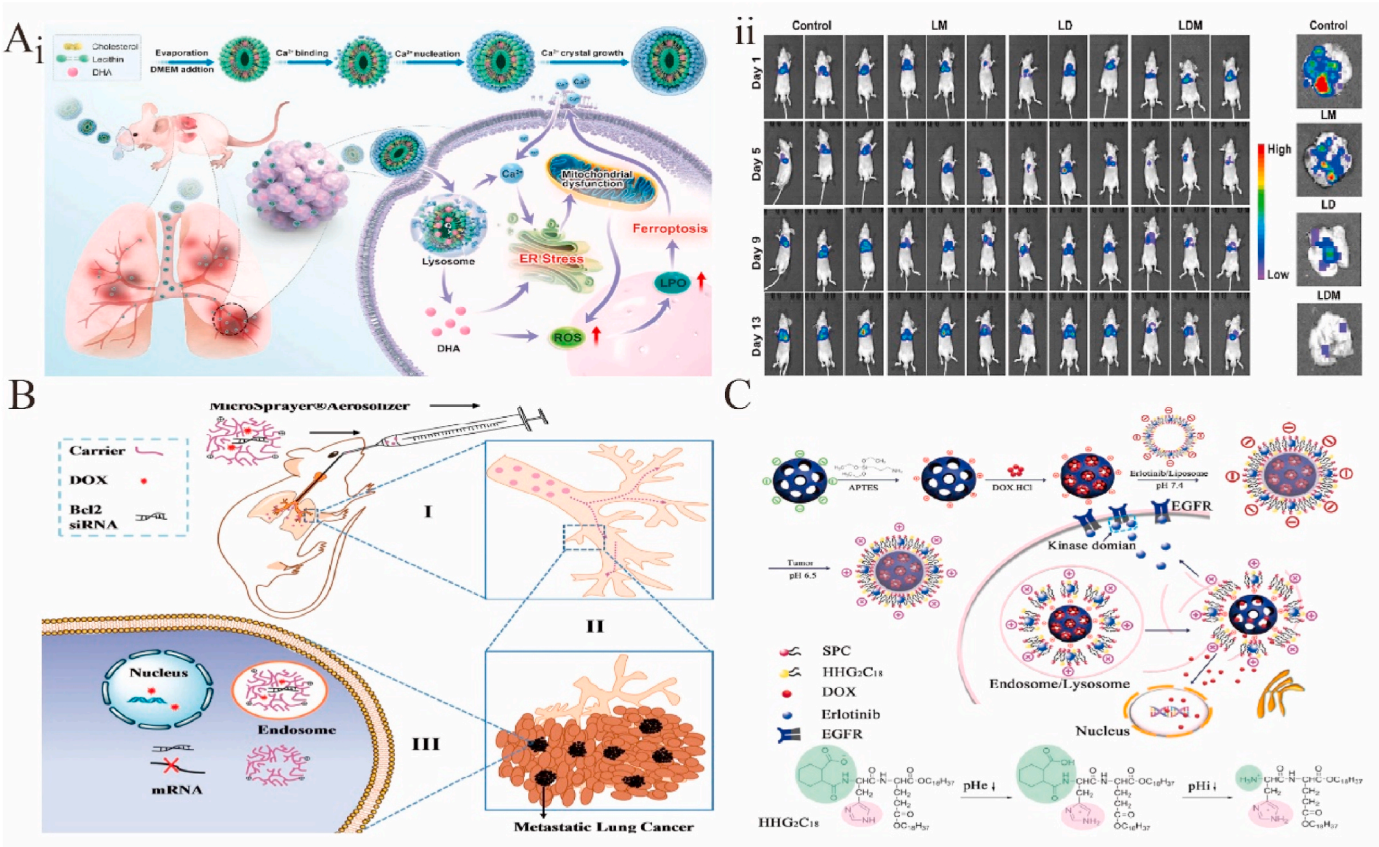

Fig. 13. Pulmonary drug delivery in lung cancer (A) Inhalable Biomineralized Liposomes for Cyclic Ca2+-Burst-Centered Endoplasmic Reticulum Stress Enhanced Lung Cancer Ferroptosis Therapy (i) Schematic illustration of a Cyclic Ca2+-Burst-Centered ER Stress Enhanced Lung Cancer Ferroptosis Therapy (ii) Relative lung tumor radiance growth curve and the tumor inhibition rate of tumor-bearing mice with different inhalation treatments. Adapted reprinted with permission from Ref. [323]. Copyright © 2023 American Chemical Society. (B) Schematic representation of co-delivery of DOX and siRNA to the lungs. Adapted reprinted with permission from Ref. [324] (License number: 5,682,860,863,312). (C) Preparation of erlotinib/DOX co-delivery nanocarriers and schematic representation of the synergistic treatment with erlotinib and DOX. Adapted reprinted with permission from Ref. [320] (License number: 5,682,870,001,416).

useful for targeting lung metastasis in immunotherapy [322]. Iron toxicity has been proposed as a potential treatment for lung cancer. Another study synthesized an inhalable biomineralized liposomal polymer for enhanced iron toxicity treatment in lung cancer by co-loading responsive calcium phosphate and dihydroartemisinin, which have good nebulizing properties. Nebulized inhalation of the polymer caused approximately 6.80-fold higher drug deposition at the lung lesion site than intravenous injection (Fig. 13A) [323]. Polyethyleneimine can form an inhalable complex with DOX and siRNA for direct delivery to the lungs, thereby increasing the deposition of DOX and siRNA in the lungs and improving apoptosis and anti-tumor effects compared with single delivery of DOX or siRNA (Fig. 13B) [324]. Kim et al. [325] used ammonium bicarbonate as a porogenic agent in the W/O/W emulsification method. Highly porous PLGA microspheres loaded with DOX and paclitaxel were prepared and powdered, and the dried microspheres showed significant anti-cancer effects in the lungs after pulmonary administration. These results suggest that DPI formulations in solid form show higher storage stability than dosage forms administered via nebulizers. However, patients with lung cancer often have poor lung function owing to lung resection surgery and chest radiation therapy, and inspiratory flow rates are usually lower than those in healthy individuals. Therefore, for the clinical application of inhaled lung cancer therapy, creating DPI dosage forms and devices that can guarantee high pulmonary delivery efficiency in patients with lung cancer despite low inspiratory flow rates is essential.

5.6. Pulmonary drug delivery in tuberculosis and progress

Mycobacterium tuberculosis is the causative agent of infectious disease tuberculosis. The disease (Tuberculosis) typically affects the lungs and can spread to other areas. Current drugs used to treat tuberculosis include rifampicin (Rif), pyrazinamide, isoniazid, and ethambutol [326]. Conventional modes of drug administration include oral and intravenous administration; however, these treatment modalities may suffer from dose limitations and first-pass effects in the liver, resulting in insufficient drug concentrations in the lungs and causing the development of drug resistance and treatment failure. Longer treatment cycles and invasive procedures leave patients without good adherence [327,328]. The direct administration of drugs to the lungs is a promising way to address these challenges. The preference for inhaled oral or intravenous formulations in patients is associated with their clinical characteristics, and inhalation may be a more acceptable method in this patient group [329]. Several types of dosage forms of anti-tuberculosis drugs have been studied. Examples include the direct delivery of anti-tuberculosis drugs via nebulized drug solutions and particulate pulmonary drug delivery formulations containing anti-tuberculosis drugs in particles [330–332]. Direct delivery of antituberculosis drugs via aerosolized liquid formulations is often unstable because they may crystallize, precipitate, or polycrystallize [333]. In contrast, powder formulations have high stability and are simpler to preserve [326]. Liposomal powders of anti-tuberculosis drugs have been extensively studied. Changsan et al. [334,335] encapsulated Rif in liposomes and delivered it to the respiratory tract [336]. Muttil et al. prepared isoniazid and rifabutin payload particles and evaluated their applicability as

dry powder inhalations targeting AM [331]. Bacterial resistance is non-negligible in treating tuberculosis, and Sharma et al. developed a mucus-penetrating particle combining the benefits of anti-tuberculosis drugs with host defense peptides to validate the potential of using a mucus-penetrating inhalable drug delivery system as a targeted pulmonary delivery vehicle (Fig. 14A and B) [337]. NPs have been considered by researchers for anti-tuberculosis inhalation therapy, in addition to advancements made with liposomal powders and microparticles. Porous NPs can effectively improve drug bioavailability and nebulization performance, and are an effective route for anti-tuberculosis inhalation therapy (Fig. 14C) [241]. Vadakkan et al. [338] developed a spray drying method that allows for the loading of Rif into respirable particles that can be broken down into nanomicelles. Similarly, human serum albumin NPs can carry benzothiazinones as solubilizing agents or as drug delivery systems for pulmonary drug delivery [339].

5.7. Pulmonary drug delivery in disease diagnosis

Drug delivery by pulmonary inhalation can be used to treat and diagnose lung diseases; it is a safe, convenient, and non-invasive diagnostic modality. GAO et al. [340] described a novel nano-inhaled contrast agent that can produce a higher signal intensity than MRI alone in diagnosing lung cancer, improving the validity and accuracy of a lung cancer diagnosis. With the application of inorganic NPs as lung delivery carriers, materials based on inorganic plasmonic and magnetic properties can be used to diagnose diseases of the respiratory system, and external magnetic fields, such as positron emission tomography,

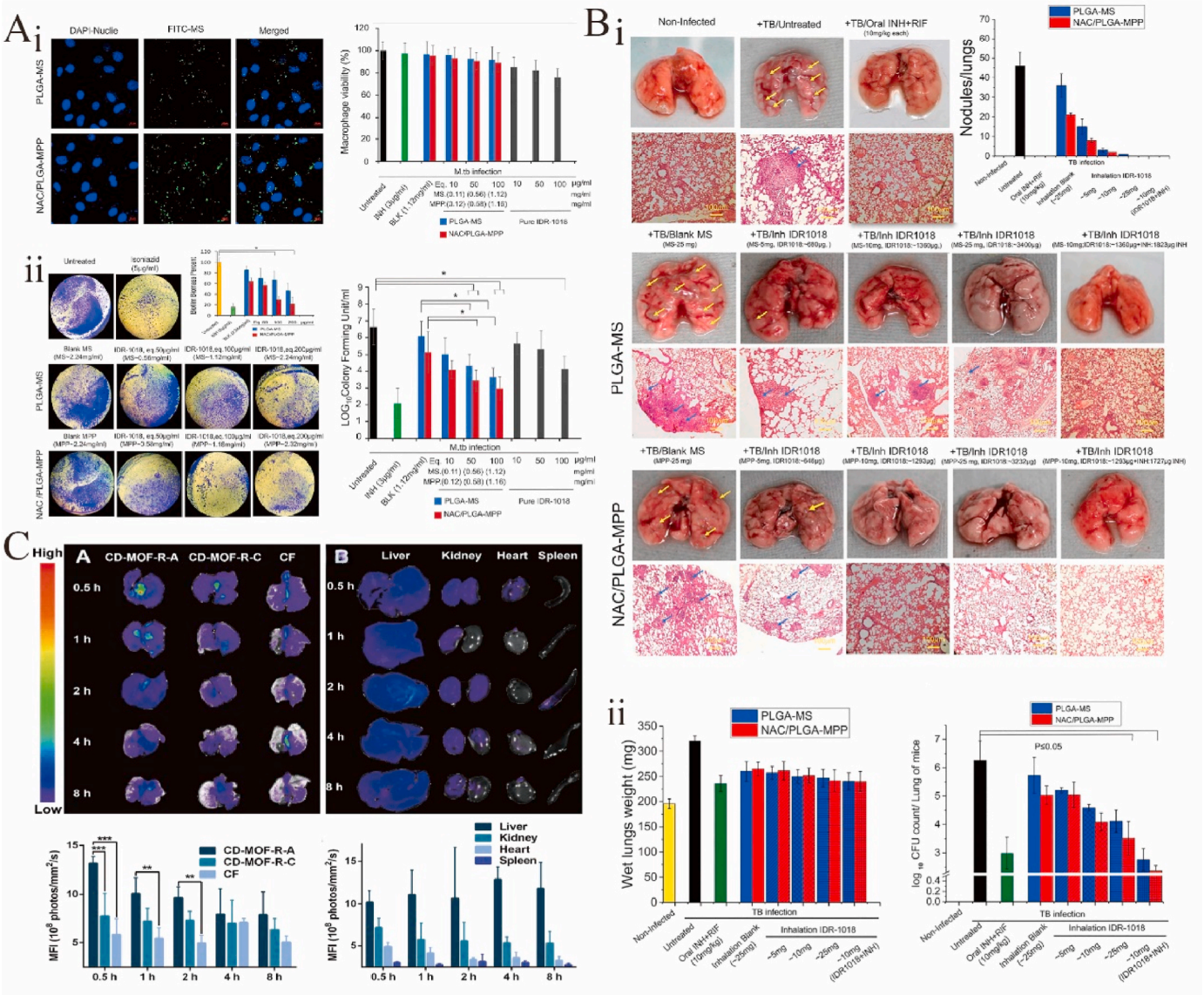

Fig. 14. Pulmonary drug delivery in tuberculosis (A) The potential of inhalable N-acetyl cysteine/poly (lactic-*co*-glycolic acid) mucus-penetrating microparticles for the treatment of lung-delivered carriers in the treatment of tuberculosis. (i) Confocal laser scanning microscope images of RAW 264.7 macrophage cells following incubation with florescent PLGA-MS (Panel-1) and NAC/PLGA-MPP (Panel-2) for 3 h showing the distribution of particles inside cells. (ii) Biofilm disruption effect of PLGA/MS and NAC/PLGA-MPP on the biofilm biomass disruption. The imaging of tubercle bacillus biofilm grown in 3 weeks of incubation. Adapted reprinted with permission from Ref. [337] (License number: 5,682,870,413,810). (B) Morphological and histopathological changes (H&E staining) (i) and statistical analyses (ii) in the lungs of mice after Mycobacterium tuberculosis infection and inhalation treatment with N-acetyl cysteine/poly(lactic-*co*-glycolic acid) mucus-penetrating-microparticles. Adapted reprinted with permission from Ref. [337] (License number: 5,682,870,413,810). (C) Fluorescence images of the lungs and other major organs (liver, kidneys, heart, and spleen) at different time points after *trans*-lung delivery of CD-MOF to rats. Adapted reprinted with permission from Ref. [241], based on CC BY License. Abbreviations: CD-MOF: cyclodextrin-based metal-organic framework.

magnetic resonance imaging, and computed tomography, can direct these magnetic NPs to target sites [341].

5.8. Pulmonary drug delivery in other systemic diseases

In addition to the effective treatment of various lung diseases, other organs and systems can be treated through pulmonary inhalation. Pulmonary and respiratory inhalation therapies for diabetes, schizophrenia, and bipolar disorder have been extensively studied. Diabetes mellitus is a severe chronic disease that develops when the body cannot produce sufficient insulin or when using the insulin it produces effectively. It is typically characterized by high blood glucose concentrations. Inhaled insulin is effective for patients with diabetes [342]. The first inhaled insulin product, Exubera®, was approved by the FDA in 2006 for the treatment of diabetes [343]. However, Exubera® was withdrawn from the market for several reasons, including high cost, complexity of the device, differences in commonly used insulins, and a possible increased risk of lung cancer [344]. Another FDA-approved inhaled insulin product, Afrezza®, was introduced in 2014. It is a DPI device reagent used for glycemic control in adult patients with diabetes. As a hypoglycemic agent delivered to the lungs to control insulin release, it was found that in type I diabetic mice implanted with acetyl urea-responsive insulin--producing cells, blood glucose levels could be normalized by inhaling acetyl urea aerosol [345]. In addition to insulin, other glucose-lowering drugs have similar potential for inhalation. The development and optimization of nanosomes for delivering glibenclamide as a hypoglycemic agent to the lungs in the inhaler dosage form have been reported, and the hypoglycemic effect of this dosage form was evaluated *in vivo* [346].

In addition to endocrine system disorders, such as diabetes, which can be treated by inhalation administration, psychiatric disorders, such as depression, can be treated using pulmonary administration. Depression may be owing to the dysregulation of 5-hydroxytryptaminergic activity, reducing the levels of 5-hydroxytryptamine in the brain [347]. Selective 5-hydroxytryptamine reuptake inhibitors, such as paroxetine, veracidone, and fluvoxamine, are first-line drugs for patients with depression [348]. In 2019, the FDA approved esketamine (the S (+) enantiomer of ketamine) for treating refractory depression [349]. It was the first antidepressant administered in spray form via the nasal and respiratory tracts. Similarly, treatment of depression with inhaled sevoflurane drugs has been reported; however, more clinical trials are needed [350]. Inhaled nitrous oxide has a rapid antidepressant effect in patients with refractory depression [351,352]. Inhaled aromatic drugs have unique advantages in treating mood disorders [353,354].

6. Conclusion and challenges

6.1. Perspective or Outlook

Drug delivery methods are long developed and are administered differently, including oral, intravenous, intramuscular, sublingual, ocular, and pulmonary administrations. Each delivery method has unique advantages and disadvantages, such as the convenience of oral administration and its low bioavailability; intravenous administration can improve bioavailability but is painful. A recent consensus that pulmonary drug delivery is a prospective delivery route has been established. The lungs have low enzymatic metabolic activity, a large surface area, and avoid first-pass effects [23,24]. These characteristics and advantages allow for targeted pulmonary inhalation drug delivery, maintenance of biological activity [64], rapid onset of action [28], reduced dose delivery, and reduced systemic side effects [26]. Similarly, for patients, pulmonary administration is better regarding compliance than intravenous and intramuscular administrations owing to the absence of pains, decreased frequency of administration, and portability of some agents. Pulmonary drug delivery allows for delivering molecules such as antibiotics, peptides, proteins, antibodies, and genes directly to the middle and lower airways as mist or powder. In addition, it has been used to treat acute or chronic lung diseases such as novel coronaviruses, lung infections, COPD, asthma, lung cancer, and tuberculosis, and studied for the diagnosis and vaccine control of pulmonary diseases.

Furthermore, pulmonary drug administration has significantly improved in treating systemic illnesses, such as diabetes and neurological conditions. Thus, the use of lung-delivered drugs for the treatment of other systemic and pulmonary diseases holds great promise. However, pulmonary drug delivery requires overcoming specific physiological barriers, which depend on the formulation processing methods, carriers, and devices. The properties of the drug formulation, size of the particles, and presence or absence of excipients are factors to be considered. According to several studies, aerodynamic quality is crucial in inhalation therapy [43]. Liposomesand NPs have been used as inhalation carriers for pulmonary drug delivery. These carriers enable drug deposition in the lungs and control the rate and site of drug release, reducing the frequency of drug administration. Among other things, nanotechnology has revolutionized pulmonary drug delivery devices. NPs in inhaled drug delivery enhance the therapeutic effect of the drug and reduce the drug dose [355], enhance the solubility of the drug, particularly in hydrophobic formulations [63,356], enhance the drug stability [357], achieve a slow drug release, prevent rapid drug clearance [358,359], and most importantly, allow for targeted drug delivery [360,361]. Advances in computer technology and pharmacokinetic modeling based on lung physiology will also aid in the development of effective lung-targeted drug delivery systems [264]. In addition, structural modification of biomolecules to reduce the molecular size, prolong their retention time in the lungs, and improve receptor binding affinity are effective strategies to improve the stability and permeability of inhaled biologics. Another major focus in future studies should be the identification of biocompatible excipients to improve the stability, absorption, and aerosol performance of inhaled biologics [362]. Similarly, drug delivery devices affect pulmonary drug delivery. Traditional pulmonary delivery devices such as nebulizers, pMDI, and DPI and the new generation of delivery devices such as SMI and Smart Inhalation Devices have their strengths and weaknesses. 3D printing is a promising strategy that has been applied not only in the manufacturing of inhalation devices and powder formulation devices but also in the prediction and evaluation of the pharmacokinetic profiles of formulations. Combining nanotechnology with optimized pulmonary drug delivery formulations and enhancing the design of inhalation devices while simultaneously using computer technology for pharmacokinetic simulations may have a bright future in pulmonary drug delivery systems. Several products are currently in clinical use (Table 4) and more products for pulmonary drug delivery are undergoing clinical trials.

6.2. Challenges

Although basic research on pulmonary drug delivery systems has made considerable progress, there remain several challenges regarding their application in clinical settings. For example, how to overcome the physiological barriers of the lungs, provide effective drug deposition at the right location, and minimize drug side effects Nanotechnology may be a good strategy, but the toxicity and safety of nanodelivery systems should be addressed, along with the safety of pulmonary drug delivery of biologics. For example, inhaled vaccines must be considered not only in terms of their effects on patients and healthcare workers but also with special attention to individuals with immunodeficiencies, who may be more susceptible to the effects of vaccines [369]. Therefore, pulmonary drug delivery requires a long-term, effective safety monitoring strategy. In terms of pharmacokinetics, the mechanism underlying drug distribution in the lungs is unclear, and the stability and efficacy of new formulations have yet to be verified. Animal testing is a viable option; however, they are unable to perform the required maneuvers of active breathing [370]. A computerized post-delivery simulation of pulmonary drug delivery, although costly, may also be an effective strategy. An ideal inhaler should deliver a precise and consistent dose to the target

Table 4
Some of the products for pulmonary delivery in the article.

Name	Device Type	Drug composition	Use	Ref
K-haler®	pMDI	inhaled corticosteroid long-acting β2-agonist	Asthma	[98]
Bevespi Aeroball®	pMDI	Glibenclamide/formoterol	COPD	[86]
Spinhaler™	DPI	cromolyn sodium	Asthma	[82]
Rotahaler™	DPI	albuterol	Asthma	
Turbuhaler	DPI	terbutaline	Asthma	
Respiclick ®	DPI	Fluticasone propionate/salmeterol xinafoate	Asthma	[72]
Flexhale	DPI	budesonide	Asthma	[363]
Pressair	DPI	Aclidinium bromide	COPD	[72]
Certihaler	DPI	Formoterol fumarate	Asthma/bronchospasm	[72]
Twisthaler	DPI	Mometasone furoate	Asthma	[72]
Ellipta®	DPI	Umeclidinium/Vilanterol	COPD	[364]
Exubera®	DPI	Insulin	Diabetes	[343]
Afrezza®	DPI	Insulin	Diabetes	[87]
Pari LC®Plus	Neb	Variable drug types	Asthma/COPD/Lunginfection	[72,365,366]
Side Stream Plus ®	Neb	Variable drug types	Asthma/COPD/Lunginfection	[365,366]
Omron U22	Neb	Salbutamol	Asthma	[110]
Respimat®	SMI	Tiotropium/Olodaterol	COPD	[85]
Electronic Breezhaler®	Intelligent inhalation device	mometasone furoate/indacaterol acetate/glycopyrronium bromide	Asthma	[367]
SmartTrack	Intelligent inhalation device	corticosteroids	asthma	[115,116,368]

region of the lungs and maintain the stability of the delivered drug. However, to date, a device that can perfectly undertake pulmonary drug delivery remains to be developed. Pulmonary drug delivery devices should be small and simple enough to be easy to use by patients to improve patient compliance [73]. The concept of "individualized inhalers" for different patient populations should also be introduced. Cost control is another important factor in the successful marketing and dissemination of inhaled drug formulations. Although several challenges remain, with the continuous efforts of scholars in related fields and the development of formulation technology and analytical level, the evaluation system of pulmonary drug delivery formulations will be improved, the application of pulmonary drug delivery will be more extensive, and more pulmonary drug delivery formulations will be applied for the treatment of pulmonary, or even systemic, diseases.

CRediT authorship contribution statement

Bin Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lin Wang:** Writing – review & editing, Writing – original draft. **Qian Yang:** Writing – review & editing, Supervision. **Yuming Zhang:** Writing – review & editing. **Tang Qinglai:** Writing – review & editing. **Xinming Yang:** Writing – review & editing. **Zian Xiao:** Visualization, Supervision. **Lanjie Lei:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation, Conceptualization. **Shisheng Li:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Data availability

Data will be made available on request.

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