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REVIEW

Natural Products-Based Inhaled Formulations for Treating Pulmonary Diseases

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Abstract: Given the unique physiological and pathological characteristics of the lung, the direct, inhalable route is more conducive to pulmonary drug delivery and disease control than traditional systemic drug delivery, significantly circumventing drug loss, off-target effects, systemic and organ toxicity, etc., and is widely regarded as the preferred regimen for pulmonary drug delivery. However, very few lung diseases are currently treated with the preferred inhaled formulations, such as asthma, chronic obstructive pulmonary disease and pulmonary hypertension. And there is a lack of appropriate inhaled formulations for other critical lung diseases, such as lung cancer and pulmonary fibrosis, due to the fact that the physicochemical properties of the drugs and their pharmacokinetic profiles do not match the physiology of the lung, and conventional inhalation devices are unable to deliver them to the specific parts of the lung. Phytochemicals of natural origin, due to their wide availability and clear safety profile, hold great promise for the preparation of inhalable formulations to improve the current dilemma in the treatment of lung diseases. In particular, the preparation of inhalable formulations based on nano- and microparticulate carriers for drug delivery to deep lung tissues, which overcome the shortcomings of conventional inhalation therapies while targeting the drug activity directly to a specific part of the lung, may be the best approach to change the current dilemma of lung disease treatment. In this review, we discuss recent advances in nano- and micron-carrier-based inhalation formulations for the delivery of natural products for the treatment of pulmonary diseases, which may represent an opportunity for practical clinical translation of natural products.

Keywords: inhaled nanoformulations, inhalation therapy, natural products, nanomedicine, pulmonary diseases

Introduction

Globally, pulmonary diseases, represented by acute respiratory infections, chronic obstructive pulmonary disease (COPD), bronchial asthma, and lung cancer, are characterized by high morbidity, mortality, disability, and treatment costs.[1] With changing lifestyles, increasing environmental pollution, unavoidable occupational exposures, the continued prevalence of tobacco use, and an aging population, the morbidity, mortality and associated disease burden of pulmonary disease are increasing year by year. There is an urgent need to discover new therapeutic approaches applicable to the physiology, pathology and anatomy of the lung to transform the current global public health challenge of preventing and treating pulmonary disease.[1,2]

Conventional modes of drug delivery inevitably limit efficacy due to degradation of the active fraction in the gastrointestinal tract or first-pass metabolism in the liver, and this systemic mode of drug delivery increases non-specific toxicity due to high drug exposure to other organs.[3] The lung is an excellent organ for drug absorption. Given its natural advantages, such as its large absorptive surface area (100–200 m^2), abundant capillaries, very short transit distance, thin alveolar epithelial layer, and slow cell surface clearance, inhalation therapy is widely recognized as the preferred regimen for pulmonary drug delivery.[4] Pulmonary delivery devices, such as dry powder inhalers (DPIs), pressurized metered dose inhalers (PMDIs), nebulizers, etc., are able to

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deliver medications locally to the lungs, dramatically improving the bioavailability of medications while fully exploiting their efficacy.[5,6] Currently, inhaled formulations have become the first-line treatment for asthma and COPD, but there are no corresponding inhaled formulations for other lung diseases, including lung cancer and pulmonary fibrosis.

Phytochemicals of natural origin hold promise for inhaled formulations to improve the current dilemma of lung disease treatment due to their wide availability and clear safety profile.[5] Given the low bioavailability of natural products and the inability of existing drug dosage forms to be delivered to the lungs in their natural form by inhalation, the use of appropriate drug delivery systems to create inhalable formulations that match the physiopathological characteristics of the lungs would be a potential solution for a wide range of lung diseases.[7] Nano-/micron-sized carriers will undoubtedly be the best choice due to their smaller size and superior aerodynamic properties, enabling site-specific release for targeted drug delivery and higher retention and lower drug loss after delivery.[8,9] In this review, we systematically summarize new ideas and approaches for the treatment of lung diseases, with a focus on lung cancer, using inhalation formulations of natural products delivered by nano-/microparticle carriers. Our goal is to draw more and more research attention to the potential and great value of natural products and inhalation therapies in the treatment of lung diseases, which promises to become a focus of translational new drug development and a new trend in clinical applications in the future.

Pharmacokinetic Process of Inhaled Formulations

The first process after inhalation is drug deposition, which can occur in the oropharynx, large airways or alveoli, and determines the site of drug action. Therefore, a key measure to improve the pulmonary bioavailability of inhaled formulations is to increase the pulmonary deposition rate, which depends on their aerodynamic equivalent diameter (Dae), inhalation flow rate, inhaler device characteristics and disease-related factors.[10] Dae has a significant impact on respiratory deposition and subsequent drug absorption: particles with a Dae of 5–10 μm are retained in the upper respiratory tract; particles in the range of 1–5 μm have excellent pulmonary deposition and distribution properties and can be deposited in the secondary bronchioles (small airways and fine bronchioles); and particles in the range of 1–3 μm are suitable for deposition in the distal part of the fine bronchioles; smaller particles, about 1 μm, can accumulate in the alveoli; however, particles smaller than 0.5 μm are not deposited in the lungs and often diffuse into the bloodstream and are expelled via the respiratory airflow.[11,12] After deposition in various parts of the lungs, the drug is either cleared, absorbed into the blood or lymphatic circulation, or metabolized.[13,14] There are several clearance mechanisms depending on the site of drug deposition, including mechanical clearance, mucociliary clearance, macrophage degradation, and metabolic clearance. In the upper respiratory tract, mucociliary clearance is the primary mode of drug removal. This mechanism is more prevalent and faster for larger particles, which are usually completely cleared within 24 hours. In the lower respiratory tract, however, alveolar macrophage uptake plays a more dominant role in limiting the efficacy of inhaled preparations. Macrophages can also be targets for the delivery of certain inhaled drugs. For example, in the treatment of infectious diseases.[14] Drug particles that successfully evade lung clearance mechanisms and dissolve in the epithelial lining fluid may subsequently be absorbed into lung tissue, with the rate of absorption depending on airway characteristics and drug properties.[10] Drugs trapped in the lung tissue are metabolized by metabolic enzymes in the lung tissue after they have exerted their effect, and are released from the lung tissue into the blood circulation depending on the hyperperfusion of the lung.[10]

Therefore, given the pharmacokinetic characteristics of drugs in the lungs, inhalation formulations that match the anatomical and physiological characteristics of the lungs can achieve the desired therapeutic effect: the first aspect is to ensure that the inhaled formulation has excellent aerodynamic properties and is able to evade the lung clearance mechanism to reach the lung tissue; the second aspect to consider is the lung exposure time of the inhaled formulation; and then it is to ensure that the inhaled formulation is able to reach the target site to exert its effect and reduce the effect on the other sites, ie strike a balance between efficacy and safety.[15] Considering the current state of medical care, drug delivery systems based on nanomaterials may be the optimal solution. Nanomaterials are characterized by their small size, large specific surface area, high surface reactivity and high adsorption capacity.[16] Nanomaterials as drug carriers can improve drug pharmacokinetics and help drugs cross physiological and pathological barriers, thereby increasing bioavailability.[17] Through active or passive targeting mechanisms, nanomaterials can increase the local concentration of drugs in lung tissue lesions, control drug release, prolong drug exposure time, and improve drug efficacy while reducing side effects.[18] And through the delicate "camouflage" can reduce the body's immune recognition and reticuloendothelial system clearance, nanomaterials can increase the retention

time of the drug in vivo, prolong the half-life of the drug, and enhance the efficacy of the drug.[19] Therefore, inhalable formulations based on nanomaterials are expected to have great potential in the treatment of lung diseases.

Determinant Characteristics of Inhaled Formulations

Inhaled drug delivery technology based on nano-/microcarriers skillfully combines aerosol technology and nanotechnology to prepare drugs into inhalation formulations that match the physiological and pathological characteristics of the lungs, and then deliver them directly to the site of action or absorption in the form of aerosols (eg powders, aerosols, inhalation mist droplets, etc.) with high speed and high efficiency.[20] Therefore, considering the anatomical, physiological and pathological characteristics of the lung, the size, shape, surface properties and aerodynamic characteristics of nano-/micron-sized particle carriers determine the deposition and bioavailability of the drug in the lung.

Particle size is an important physical characteristic of inhaled formulations because it determines the properties of the aerosol as well as the site of particle action, and is classified as geometric diameter (physical diameter) and Dae (diameter of a spherical particle per unit density that settles in air at the same rate as a given particle).[21] Nanomaterials can cross the mucosal barrier due to their small size, but the choice of specific size varies. In general, for pulmonary diseases such as asthma, COPD or pulmonary infections, carriers around 200–500 nm are appropriate, as they allow rapid delivery to deeper regions of the lung and thus to target cells such as alveolar macrophages for effective intracellular delivery. Sizes smaller than 200 nm or larger than 6 μm can avoid clearance by alveolar macrophages and are more suitable for non-obstructive lung diseases such as lung cancer.[22]

Particle morphology, ie the surface roughness and external shape of particles and the internal structure of porous particles, is another important factor affecting the performance of inhalation formulations. Large shape factor and low density reduce the Dae of particles, and in general, elongated particles have a larger shape factor, resulting in a smaller Dae than spherical particles of the same volume.[21] Surface roughness or porous particles reduce interparticle cohesion, contact area and give the particles high dispersibility. In addition, the pollen-shaped particles exhibit better flowability, higher emitted dose, and higher fine particle fraction (FPF) than spherical, needle-like, plate-like, etc. particles due to their lower packing density as well as conical protrusions that increase the distance between particles, thereby minimizing interparticle forces and aggregation tendency.[23]

The surface properties of the particles are also a key determinant of the bioavailability of inhaled formulations. Nanoparticles with a high cationic surface charge have excellent stability and ability to penetrate the lung, but at the same time can cause toxic effects. Therefore, the toxicity of nanoparticles is generally avoided by using neutral or negative surface charges. Accordingly, materials such as chitosan can be used to surface modify nanoparticles to improve their ability to penetrate mucus and reduce lung clearance.[24] Conversely, for infectious diseases such as tuberculosis or pneumonia, it is recommended that nanoparticles be modified with positively charged compounds to enhance macrophage uptake. In addition, particles can be modified with pulmonary surfactants, proteins or peptides to improve biocompatibility and efficiency of drug delivery to the lungs, particularly to target specific cells such as cancer cells.[25,26]

Natural Product Components in Inhaled Formulations

Pulmonary drug delivery has become a modality of administration that has received much attention, and a large number of clinical trials are attempting to convert existing orally or intravenously administered chemicals into inhaled formulations (Table 1). Although many diseases can be treated with the advantages of pulmonary drug delivery, currently only asthma and COPD can be treated with preferred inhaled formulations, such as inhaled glucocorticoids and bronchodilators. However, other critical lung diseases such as lung cancer, pulmonary fibrosis, tuberculosis and pneumoconiosis still lack appropriate inhaled formulations due to the fact that the physicochemical properties of conventional drug dosage forms and their pharmacokinetic profiles do not match the physiology of the lung and conventional inhalation devices are unable to deliver them to the specific parts of the lung. Therefore, there is a need to develop formulations specifically for inhalation, combining optimal inhaled drugs with well-designed inhalation devices to achieve efficient and safe lung-specific therapies.[27] The use of nano- and microparticulate carriers to deliver drugs to their targets, especially in cancer, has gained unprecedented benefits over the past decades.[20,28] Therefore, the development of inhaled formulations based on nano- and microparticulate carriers to deliver drugs to deep lung tissues, which overcome the

Table 1 Clinical Trials of Inhaled Chemical Formulations for Pulmonary Diseases

Diseases	Drugs	Inhaled Formulations	Dose	Effects	Registration Number	Refs
COVID-19	N-acetylcysteine	N-acetylcysteine inhalation spray (@sinadarou.co)	One puff (200 μg per puff) every 12 h for 7 days	↓The mortality rate, inflammatory parameters, and the development of severe respiratory failure	An open-label randomized controlled clinical trial (IRCT2008090100116 5N55)	[30]
Pulmonary hypertension	Treprostinil	Treprostinil	0.6 mg·mL−1 via an ultrasonic pulsed-delivery nebuliser at 6 μg per breath for 108 weeks	↑Exercise capacity and FVC	An open-label extension study (NCT02633293)	[31]
Idiopathic pulmonary fibrosis	Pirfenidone	Inhaled pirfenidone solution	50 mg once per day: n=46, 100 mg two times per day: n=45 for 72 weeks	↓Side effects of pirfenidone	A phase 1b, randomised, open-label, dose-response trial (ACTRN12618001838202)	[32]
Ventilator-associated pneumonia	Colistin	Conventional jet nebuliser continuously nebulizes colistimethate sodium	500 000 U colistin, thrice daily, for the first 10 ICU days or until extubation.	↑ICU survival rate	A single-centre, two-arm, randomised, open-label, controlled trial (NTC01025921)	[33]
Cystic fibrosis	Mannitol	Inhaled dry-powder mannitol	(10×40 mg) twice daily for 12 consecutive days.	↑Peripheral airway function	A double-blind, randomised, placebo-controlled pilot study (ACTRN 12612001167853)	[34]
Non-cystic fibrosis bronchiectasis	Ciprofloxacin	Ciprofloxacin dry powder for inhalation	32.5 mg, twice daily for 28 days	↓The total bacterial	A Phase II, randomised, double-blind, multicentre study (NCT00930982)	[35]

Notes: ↑, increase or promote; ↓, decrease or inhibit.

shortcomings of traditional inhalation therapies while targeting drug activity directly to specific parts of the lung, may be the best way to change the current dilemma of lung disease treatment.[29]

Frustratingly, in today's era of drug discovery, a large number of chemically synthesized molecules are approved and marketed by regulatory agencies that have good therapeutic value, but resistance, side effects, etc., remain unavoidable problems and are not always suitable for preparation into inhaled formulations. Unlike oral administration, inhaled formulations should have low oral bioavailability and high systemic clearance to maximize airway selectivity and minimize toxicity associated with systemic exposure after drug inhalation.[36] Phytochemicals of natural origin may help to address these issues. Plants have been an important source for drug development and translational medicine since ancient times due to their abundance, high safety profile, and multiple mechanisms of action.[37] However, the clinical applicability of phytochemicals is often hampered by their low bioavailability, which may be associated with their low solubility and/or susceptibility to degradation in aqueous media. For example, the bioavailability of quercetin in humans after oral administration was as low as 1%, which was attributed to poor aqueous solubility (2.84 mg/mL).[38] In addition, the insoluble flavonoid silibinin is characterized by limited oral absorption (<50%), resulting in weak clinical efficacy.[39] Therefore, the properties of natural products such as low oral bioavailability and high safety profile are the advantages for their preparation into inhaled formulations. Nano-delivery systems containing natural phytochemicals have no first-pass effect, rapid onset of action, high bioavailability, high local drug concentration at low dosage, enhanced pharmacological activity and higher safety margins (Figure 1). Consequently, pulmonary natural product delivery systems based on inhalable nano/micron carriers such as liposomes, nanoparticles, microparticles, nanocomposites, and nanoaggregates and (Figure 2) would be an attractive method of pulmonary drug delivery.

Inhaled Nanoformulations Based on Natural Products

Lipid-Based Inhaled Nanoformulations

Lipids are important components in living organisms, including fats, phospholipids, and sterols, of which phospholipids and sterols are the major components of biological membranes.[40] Compared with other nanoformulations, it uses biocompatible lipid materials (eg, triglycerides and fatty acids) as carriers to dissolve or encapsulate the drug in the lipid core or adsorb it on the surface of the nanoparticles, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), etc., and it has good biocompatibility, complete biodegradability as well as low carrier toxicity and immunogenicity.[41] Lipid-based nanomedicines are the forerunners in the clinical translation of nanomedicines, and most of the currently marketed nanomedicines are lipid-based nano-delivery systems represented by liposomes, which are widely used in the fields of cancer therapy, viral or fungal infections, analgesia, gene delivery, etc.[42,43] Inhalable lipid nanoformulations based on natural products also show excellent potential in the treatment of pulmonary diseases (Table 2).

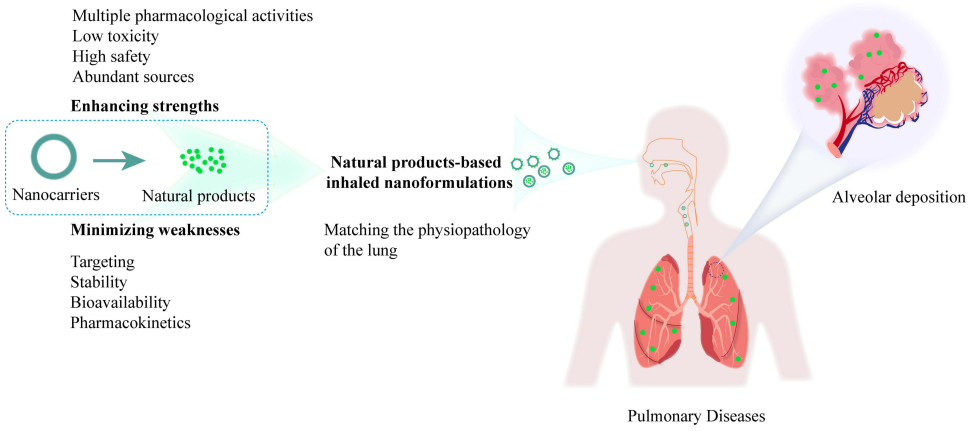

Figure 1 Benefits of natural product-based inhaled nanoformulations in the treatment of pulmonary diseases.

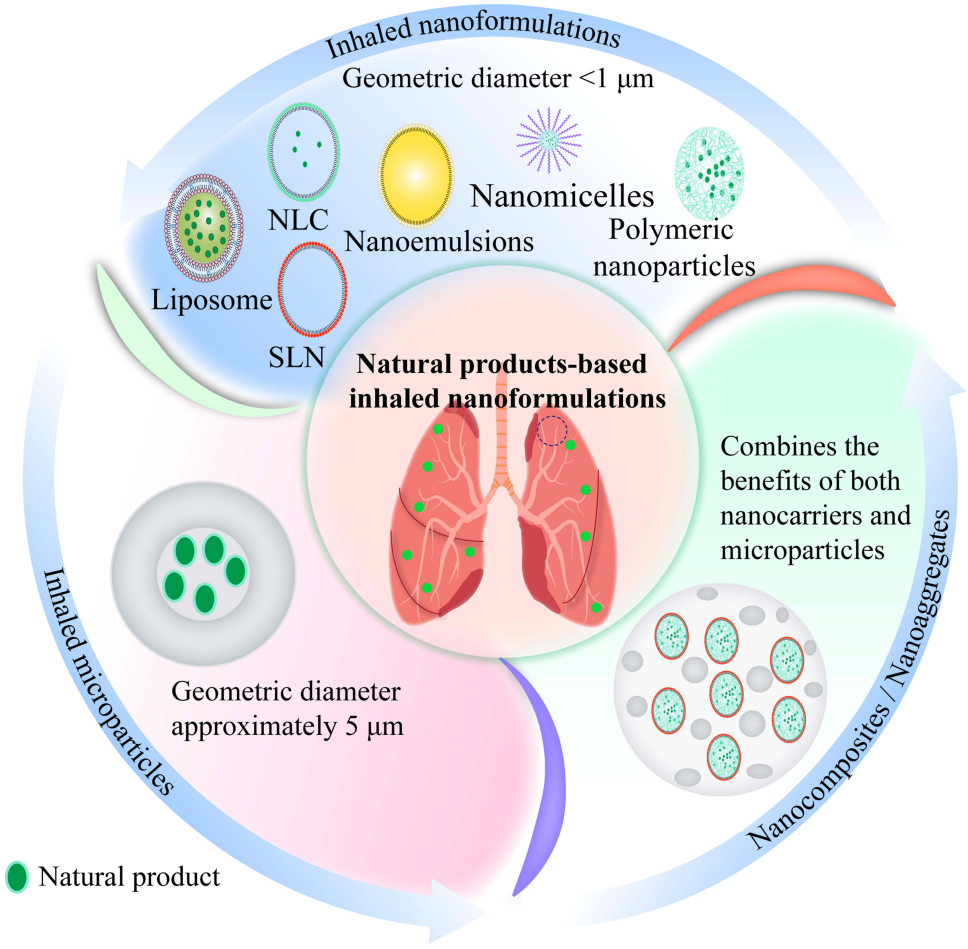

Figure 2 Drug delivery nano/micron carriers for natural products.

Liposomes

Liposomes are the earliest and most successful inhalable lipid nanocarriers, and liposomal formulations can be delivered to the lungs either by nebulizer atomization or as a dry powder via DPI.[12] Liposomes are spherical vesicles (usually in the range of 20 nm to 20 μm) consisting of an aqueous core surrounded by one or more phospholipid bilayers of natural or synthetic origin, capable of encapsulating and carrying both hydrophilic (aqueous core) and lipophilic (lipophilic bilayers) drugs to achieve precise drug release at the site of the lesion.[77] Enhanced pulmonary drug delivery through improved pharmacokinetics and pharmacodynamics, liposomes increase drug therapeutic index, improve patient compliance, reduce respiratory side effects and decrease drug toxicity.[15] Liu[78] et al demonstrated that liposomes promote rapid pulmonary distribution and cytoplasmic release of cyclic guanosine monophosphate-adenosine monophosphate, stimulate STING signaling and type I interferon production in pulmonary antigen-presenting cells, and induce systemic anticancer immunity and long-term inhibition of lung metastasis. A 2015 clinical study also found that cystic fibrosis patients who received a formulation of nebulized DNA plasmid-liposome complexes encoding the CFTR gene every 28 days for 12 months improved lung function with a 3.7% increase in forced expiratory volume in 1 s (0.07%-7.25%).[79] In studies of inhaled formulations for the treatment of lung diseases, natural products have shown low side effects, stable anti-inflammatory and antifibrotic therapeutic effects, and no significant drug dependence due to their natural properties, making them promising therapeutic alternatives to inhaled therapies.[5]

Increasing respiratory infections and hard-to-beat pathogens (eg, multidrug-resistant strains) have become a challenge in clinical practice, and conventional antibiotic therapies are increasingly ineffective due to limitations in tissue penetration, toxicity, or drug resistance.[77] In a mouse model of *Staphylococcus aureus*-induced pneumonia, DPI

Table 2 Natural Products-Based Lipid Inhaled Nanoformulations for the Treatment of Pulmonary Diseases

Nanocarrier	Natural Products	Nanoformulation	Diseases	Size (nm)	Aerodynamic Diameter (μm)	Zeta Potential (mV)	Polydispersity Index (PDI)	Mechanism	Refs
Liposomes	Andrographolide	Liposomal andrographolide dry powder inhalers	Pneumonia	77.91±22.91	4.87	−56.13 ± 3.33	0.22 ± 0.04	↓Inflammation and regulated the immune reaction	[44]
	Oxymatrine	Chitosan-coated liposome loaded with oxymatrine	Pneumonia	246.16±3.03	–	−14.54±3.04	0.208 ± 0.018	↓Viral replication	[45]
		Carboxymethyl Chitosan Modified Oxymatrine Liposomes	Emphysema	228.82 ± 4.53	–	7.65 ± 1.09	< 0.3	↑Anti-inflammatory and antioxidative effects	[46]
	Naringin	Endogenous surfactant-based liposomal delivery system of naringin	Pulmonary fibrosis	171.4 ± 5.8	2.35 ± 1.02	−15.5 ± 1.3	0.2 ±0.012	↓Lactate dehydrogenase activity, total protein content, and inflammatory cell infiltration	[47]
	Cholesterol	Liposomal dry powder inhaler formulation loaded with oxymatrine cholesterol and budesonide	Pulmonary fibrosis	<100	4.68 ± 0.26	−36.9 ± 0.6	–	↑Drug retention (more than 24 h) ↓systemic exposure	[48]
	Paclitaxel	Dilauroylphosphatidylcholine liposomal formulations	Pulmonary metastases in murine renal carcinoma model	–	–	–	–	↓Lung weights and number of visible tumor foci	[49]
		Paclitaxel-in-liposome-in-bacteria	Lung cancer	64.3 ± 2.4	–	−9.96 ± 0.48	0.35 ± 0.08	↓VEGF and HIF-1α; ↑The expressions of immune markers and immune cells	[50]
	Docetaxel	Docetaxel-loaded folic acid-conjugated liposomes	Lung cancer	100.1 ± 1.0	–	−28.6 ± 2.6	0.229	↑Cellular uptake and higher drug exposure	[51]
	Hydroxycamptothecin	Cationic liposomal hydroxycamptothecin	Lung cancer	67.57 ± 14.22	–	10.10 ± 0.40	0.34 ± 0.03	↑Apoptosis and the production of reactive oxygen species	[52]
	Vincristine	Spray-dried powders containing vincristine-liposomes	Lung cancer	112.6 ± 3.7	–	−21.56 ± 2.53	0.266 ± 0.017	↑The bioavailability of vincristine	[53]
	Camptothecin	Dilauroylphosphatidylcholine liposome aerosols containing 9-nitrocamptothecin	Lung cancer	–	–	–	–	↑Drug deposition in the lungs	[54]
			Lung cancer	About 100	1.2–1.6	–	–	↑Drug deposition in the lungs	[55]
			Lung cancer	–	–	–	–	↓Visible and microscopic disease ($P < 0.02$), the total number of tumor foci in the lungs	[56]
			Lung cancer	–	–	–	–	↓Tumor metastases in the lungs.	[57]

(*Continued*)

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Table 2 (Continued).

Nanocarrier	Natural Products	Nanoformulation	Diseases	Size (nm)	Aerodynamic Diameter (μm)	Zeta Potential (mV)	Polydispersity Index (PDI)	Mechanism	Refs
Proliposomes	Curcumin	Spray-Dried Proliposomes for the delivery of curcumin	Lung cancer	164.15 ± 6.86	2.10 ± 0.26	34.95 ± 3.18	0.40 ± 0.04	↑The ability to reach deep lung tissues	[58]
Liposomes	Curcumin	Liposomal curcumin dry powder inhalers	Lung cancer	94.65±22.01	5.81	–	0.26±0.01	↑Anti-oxidative and anti-inflammatory effects, and apoptosis	[59]
		Liposomes co-loaded with amphiphilic TAT-PEG-SN38 and curcumin	Lung cancer	171.21 ± 1.10	–	−5.96 ± 0.32	0.124 ± 0.03	↑Antiproliferative effect, apoptosis, and cell cycle arrest	[60]
	Dihydroartemisinin	Biomineralized liposome co-loaded with dihydroartemisinin and pH-responsive calcium phosphate	Lung cancer	146.27±1.86	–	−17.9 ± 0.3	0.236± 0.009	↑Ferroptosis	[61]
	Quercetin	Transferrin receptors targeting peptide surface-functionalized liposomes	Lung cancer	84–114	–	–	0.097–0.22	↑Cytotoxicity, apoptosis, and S-phase cell-cycle arrest.	[62]
	Triptolide	Carbonic anhydrase IX surface-functionalized liposomes	Lung cancer	160.1 ± 0.9	–	–	0.175 ± 0.010	↑The cellular uptake efficiency	[63]
Solid lipid nanoparticles	Paclitaxel	Solid lipid nanoparticles with modified new folate-grafted chitosan derivative	Lung cancer	249 ± 36	–	+32 ± 1	0.31 ± 0.02	↑Pulmonary exposure ↓Half-maximum inhibitory concentrations	[64]
	Myricetin	Inhalable microparticles comprising MYR solid lipid nanoparticles	Lung cancer	75.98	2.39	−22.5	1.84	↑Cellular uptake and antitumor activity	[65]
	Naringenin	Naringenin-loaded solid lipid nanoparticles	–	98±0.61	–	−31.4±0.98	0.258±0.058	↓The bioavailability	[66]
Nanostructured lipid carriers	Paclitaxel	Cremophor EL loaded nano-lipid carriers containing paclitaxel and doxorubicin	Lung cancer	394.1 ± 5.6	1.60–2.21	_18.17 ± 2.	0.180 ± 0.02	↑Retention and drug accumulation; ↓The toxic consequences in non-target tissues	[67]
		Luteinizing hormone-releasing hormone- nanostructured lipid carriers-siRNAs- paclitaxel nanoparticles	Lung cancer	111.3 ± 20	–	+45	–	↓Tumor growth and adverse side effects	[68]
		Luteinizing hormone-releasing hormone- nanostructured lipid carriers-siRNAs- paclitaxel nanoparticles	Lung cancer	110 ±20	–	+45.5	0.4	↓Tumor growth and adverse side effects	[69]

Nanoemulsion	Tea tree oil	Tea tree oil nanoemulsion	Bacterial and fungal pneumonia	12.5±0.5	–	−20.7±7.3	0.47±0.03	↓Lung injury, leukocyte recruitment, and pro-inflammatory mediators	[70]
	Tanshinone IIA	Tanshinone IIA -nanoemulsion formulation based on rhamnolipid biosurfactant and tea-tree oil	Acute lung injury	105.7 ± 0.9	–	−29.5 ± 1.8	0.31 ± 0.02		[71]
	Quercetin	Oil-in-water (O/W) nanoemulsion system	Lung cancer	131.4 ± 0.72	3.09 ± 0.05	−51.1 ± 0.28	0.257 ± 0.00	↑Cytotoxicity and stability	[72]
	Docetaxel	Docetaxel -loaded nanoemulsion formulation	Lung cancer	94.35 ± 0.77	3.02 ± 0.26	− 38.64 ± 1.43	–	↑Cytotoxicity and stability	[73]
	Naringin	Naringin- and celecoxib-Loaded nanoemulsion	Lung cancer	75–106	4.88 ± 0.11	−3.42 to −4.86	0.46–0.55	↑Stability profiles and cytotoxicity	[74]
	Curcumin	Docetaxel- and curcumin-Loaded nanoemulsions	Lung cancer	95.80/ 96.94	3.19 ± 0.15/ 3.08 ± 0.15	−36.23/ −33.40	0.25/ 0.22	↑Favorable physicochemical and aerodynamic pulmonary delivery properties	[75]
		Docetaxel- and curcumin-Loaded nanoemulsions	Lung cancer	104.70/ 101.23	4.6–5.5	−38.10/ −36.83	0.26/ 0.18	↑Favorable physicochemical and aerodynamic pulmonary delivery properties	[76]

Notes: ↑, increase or promote; ↓, decrease or inhibit.

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delivered andrographolide liposomes to the lungs, which inhibited lung inflammation, immune responses, and tissue damage by downregulating the NF-κB pathway and the release of pro-inflammatory cytokines such as TNF-α and IL-1. Moreover, andrographolide liposomes delivered to the lungs showed stronger antibacterial effects against pneumonia compared to tenfold doses of andrographolide or penicillin.[44] Similarly, oxymatrine (OMT) derived from *Sophora flavescens* Ait has excellent anti-inflammatory, antioxidant, and antiviral activity. However, OMT is a hydrophilic natural phytochemical that tends to diffuse in the mucus layer and penetrate the air-blood barrier to rapidly enter the circulation, limiting its efficacy.[45,46] Chitosan, which is highly biocompatible and biodegradable, and its encapsulated liposomes deliver OMT directly to the lungs, enhancing its distribution and retention in lung tissue without mucus restriction, thereby inhibiting the biosynthesis and penetration of human respiratory syncytial virus to exert its antiviral effects.[45] Moreover, liposomes further enhanced the anti-inflammatory and antioxidant effects of OMT by down-regulating inflammatory cytokines and modulating the rebalancing antioxidant/oxidant Nrf2/HO-1 and NF-κB/IκB-α signaling pathways, which alleviated alveolar dilatation and destruction in emphysema model mice.[46]

Pulmonary fibrosis (PF) is a common, progressive, irreversible, and fatal chronic lung disease characterized by excessive structural remodeling of lung tissue due to myofibroblast proliferation and extracellular matrix deposition that impairs alveolar elasticity and lung function, ultimately leading to severe functional failure and even death.[80] Kotta et al[47] designed a liposomal naringin based on endogenous surfactant (phosphatidylcholine) to deliver naringin as an aerosol to the deep alveoli to attenuate inflammatory cell infiltration, oxidative stress, and collagen deposition to reduce alveolar surface tension thereby maintaining airway patency. In addition, the combination regimen may have a better antifibrotic effect. Co-loading of inhaled corticosteroid (budesonide) and antifibrotic natural product (colchicine) in liposomes and delivery to deep lung tissues as a dry powder using DPI, which can achieve site-specific delivery, reduce systemic exposure and prolong drug residence time in the lung (more than 24 hours), thus synergistically improving fibrotic lesions.[48]

Although conventional therapies have shown clear benefits in the treatment of cancer, a number of factors, including chemotherapy-induced toxicity and adverse effects, lack of target specificity, and most importantly, drug resistance during cancer progression, limit the clinical efficacy in lung cancer.[81] Pulmonary delivery of natural products based on inhalable nanoformulations reduces drug dosage, decreases systemic toxicity and increases the actual local concentration of the drug in the lungs, ultimately resulting in better anti-tumor efficacy. Currently, marketed plant-derived chemotherapeutic agents such as paclitaxel,[49,50] docetaxel,[51] camptothecin,[52,54–56] and vincristine[53] have been prepared in their inhalable liposome nanoformulations for deep drug delivery and pulmonary therapy.

Paclitaxel is the most successfully developed plant-based chemotherapeutic agent, but its high lipophilicity limits its solubility in aqueous media, which in turn affects the efficacy of oral and intravenous administration. Liposomes can overcome this challenge by improving pharmacological properties and reducing toxicity.[82] Paclitaxel was encapsulated in a liposomal formulation of dilauroylphosphatidylcholine, and pharmacokinetic studies showed that the area under the curve for inhalation administration was 26 times greater than that for intravenous tail vein administration. In an established mouse model of lung metastasis from renal cell carcinoma, inhalation of a liposomal formulation of paclitaxel via a nebulizer significantly reduced lung weight and the number of tumor foci in mice, while also demonstrating improved long-term survival.[49] Interestingly, Zhang et al[50] used live carrier bacteria for targeted delivery of paclitaxel. Liposomal paclitaxel was efficiently internalized into bacteria (*Escherichia coli* or *Lactobacillus casei*) by electroporation without affecting the growth of these bacteria. After intratracheal administration, the distribution of drug-carrying bacteria was much higher in the lung than in other organs, resulting in faster delivery of the carrier to lung cancer cells, which in turn downregulated vascular endothelial growth factor and HIF-1α and induced apoptosis. In addition, drug-carrying bacteria significantly increased the expression of immune markers (TNF-α, IL-4, and IFN-γ) and immune cells (leukocytes and neutrophils), resulting in superior anticancer activity.[50]

It has been found that aerosolized inhalation can disrupt the structure of liposomes and affect the final efficacy, which can be modified by preparing them as stable dry powder formulations by spray-drying, spray-freeze-drying and freeze-drying.[12] Docetaxel is a natural antitumor compound similar in structure and efficacy to paclitaxel. Zhu et al[51] first prepared folic acid-conjugated liposomes loaded with docetaxel, followed immediately by an inhalable dry powder using spray drying technique, which showed higher cellular uptake, cytotoxicity, tumor targeting properties and drug exposure accompanied by low drug exposure in other organs. Similarly, the use of spray-drying technology to produce liposomes

of vincristine that can be administered via DPI to increase its exposure in the lungs and reduce clearance time imparts better anti-tumor properties to vincristine.[53]

Since camptothecins are alkaloids with excellent anticancer activity, and the potent anticancer agents irinotecan and topotecan are derivatives of these alkaloids, the continued development of comedones and their derivatives holds the promise of continued superior efficacy.[83] 9-Nitrocamptothecin (9-NC, a derivative of camptothecin) is a water-insoluble anticancer drug. After 30 min of inhalation of 9-NC liposomal aerosol, a large amount of the drug accumulated in the lungs (310 ng/g), while relatively little accumulated in other organs.[54] Inhaled 9-NC liposome aerosol reduces lung weight, number of tumor foci and size of individual tumor nodules in mouse models of melanoma and osteosarcoma lung metastases.[55,56] In contrast, oral 9-NC liposome had no detectable effect on cancer growth, suggesting that its therapeutic benefit is due to lung deposition.[55] Mutations in the P53 oncogene have been found in most lung cancers, leading to increased drug resistance and tumor recurrence. Transfer of the P53 gene into tumor cells to induce apoptosis and increase cellular sensitivity to chemotherapeutic agents may be a potential solution. Aerosol pulmonary delivery of polyethyleneamine-p53-DNA (PEI-p53) complexes can achieve high levels of p53 gene expression to inhibit the growth of lung metastases.[84,85] More importantly, the sequential aerosol delivery of PEI-p53 and 9-NC liposome showed significant synergistic efficacy in inhibiting the growth of established melanoma metastases in the lung, reducing the dose of drugs used and increasing the average survival time of the mice by 30–40%.[57] This combination regimen also includes sonodynamic therapy. Xiao et al[52] combined pulmonary delivery of cationic liposomal hydroxycamptothecin-based chemotherapy and 5-aminolevulinic acid-based sonodynamic therapy, again showing significant synergistic efficacy. This combined regimen showed enhanced cytotoxicity by inducing apoptosis and increasing reactive oxygen species (ROS) production in cancer cells, suggesting that inhaled therapies may be suitable for the development of combination regimens for lung cancer.

Curcumin is a naturally occurring polyphenol extracted from the rhizome of *Curcuma longa*, which limits its conversion into an anticancer agent due to its low hydrophilicity, poor bioavailability and rapid clearance from the body.[86] Liposomal curcumin nanoformulations exhibit excellent atomization properties that promote the delivery of curcumin to deep lung tissues, increase the rate and extent of lung tissue uptake, and prolong exposure time in lung tissues.[58] After freeze-drying, curcumin liposome dry powder was prepared, which was suitable for lung inhalation and selective targeting of lung cancer cells, and showed superior anticancer activity to gemcitabine and curcumin powders due to its high lung deposition with an average FPF of 46.71 and Dae of 5.81 μm.[59] In addition, liposomes co-loaded with curcumin and 7-ethyl-10-hydroxyl camptothecin precursors showed enhanced anti-proliferative, pro-apoptotic and cell cycle inhibitory effects to synergistically inhibit lung cancer growth compared to the single agent.[60]

Ferroptosis therapy has been proposed as a promising strategy for lung cancer treatment by promoting intracellular ROS production and lipid peroxidation accumulation (LPO).[87] However, insufficient intracellular ROS levels and suboptimal drug accumulation in cancer tissues hamper the effectiveness of iron death therapy, and the respirable biomineralized liposomes constructed by Fu et al helped to improve the situation through intracellular ROS and LPO accumulation-driven cell swelling and cell membrane disruption.[61] The natural product dihydroartemisinin (DHA) was doped into the liposome core, while pH-responsive calcium phosphate (CaP) was coated on the liposome surface as a shell. Upon aerosolized delivery to lung tumors, the CaP shell disintegrates and releases a certain amount of Ca^{2+} into the cell, triggering an initial Ca^{2+} burst. Meanwhile, the intense endoplasmic reticulum stress induced by Ca^{2+}, aided by DHA-mediated ROS generation and sarco-/endoplasmic reticulum calcium ATPase inhibition, can further promote LPO generation and ferroptosis, which in turn accelerates tumor elimination both in vitro and in vivo.[61]

To enhance antitumor drug-specific delivery and avoid off-target effects, active targeting is an effective strategy.[88] T7 peptide is a cell-targeting peptide with specific binding affinity for the transferrin receptor (TFR), and targeting of the TFR, which is overexpressed and confined to tumor cells, may increase the therapeutic efficacy in lung cancer.[89] The T7 surface is functionalized with loaded quercetin liposomes that are actively targeted for delivery to lung cancer cells, which in turn release quercetin to induce apoptosis, S-phase cell cycle arrest and growth inhibition of tumor tissue. Its accumulation and sustained release behavior in the lung lasted up to 96 hours without systemic toxicity.[62] Similarly, Lin et al[63] used carbonic anhydrase IX, an enzyme expressed on the surface of lung cancer cells, to surface-modify liposomes loaded with tretinoin lactone to specifically target and kill lung cancer cells.

Solid Lipid Nanoparticles (SLN)

SLN are colloidal dispersions of non-polar lipids (eg, triglycerides and fatty acids) composed of excipients that are "generally recognized as safe". SLN are solid at both room and body temperatures, which reduces the mobility of the delivered drug in the lipid matrix and improves its stability and sustained release efficiency. In contrast, SLN have a greater affinity for lipophilic drugs.[90] Rosière et al[64] developed inhalable SLN highly loaded with paclitaxel and modified with folic acid and chitosan to improve surface properties. Lung exposure to paclitaxel was prolonged up to 6 h after inhalation administration with limited systemic distribution. In addition, folic acid-modified SLN enhanced the selectivity of SLN for lung cancer cells by actively targeting the folate receptor on the surface of lung cancer cells, which in turn penetrated and distributed throughout the lung tumors independently of the vasculature.[64] This vascular low-dependence therapeutic regimen will have positive implications for poorly vascularized solid tumors such as lung cancer.

Attributed to its limited water solubility (2 mg / mL), the bioavailability of myricetin is poor, which restricts its further drug development and clinical application.[91] Based on phospholipid complexes, SLN encapsulating myricetin were prepared, which could ensure the high stability of myricetin and at the same time endow myricetin with faster drug release and uptake as well as more significant antitumor activity against lung cancer cells. After spray drying, the aerodynamic particles were produced with an mass median aerodynamic diameter (MMAD) of 2.77 μm, indicating that they could be deposited in the target bronchial area for targeted treatment of lung cancer.[65] Similarly, Peng et al[66] successfully incorporated the poorly water-soluble drug naringenin into SLN for pulmonary delivery using emulsification and low-temperature hardening methods, significantly improving the bioavailability of naringenin by 2.53 times that of naringenin suspension.

Nanostructured Lipid Carrier (NLC)

NLC is a new type of nano-drug delivery system developed and formed on the basis of SLN. Through the introduction of liquid lipid carrier, compared with SLN, it has higher encapsulation rate, drug loading capacity and stability, which can effectively increase the solubility of drug, prolong the action time of drug in vivo, improve the bioavailability and reduce the adverse drug reactions.[92] Inhalation of surfactant Cremophor EL-based NLCs enhances cellular uptake and drug accumulation of paclitaxel and doxorubicin in lung cancer cells, improving drug resistance while reducing toxicity to non-target tissues.[67] Moreover, the use of NLC as a multifunctional nanomedicine platform can enable multiple mechanisms of lung cancer treatment.[68,69] Garbuzenko et al[68] fabricated a multifunctional delivery NLC co-loaded with paclitaxel and small interfering RNAs (siRNAs). The NLC enhances drug stability, solubility, and cellular penetration. The inhalation delivery technique delivers the drug to the lungs to promote passive targeting and uses luteinizing hormone-releasing hormone (LHRH) modification, a molecule specific for targeting receptors overexpressed in the plasma membrane of lung cancer cells, to actively target lung cancer cells. The system delivers paclitaxel to induce cancer cell death and a series of siRNAs to inhibit all four types of epidermal growth factor receptors - tyrosine kinases. In addition, the formulation exhibits desirable organ accumulation, superior anticancer activity and significantly fewer side effects than single agents or siRNA or non-targeted delivery.[68] Similarly, Taratula et al[69] developed multifunctional NLC for pulmonary co-delivery of chemotherapeutics and siRNAs. LHRH-modified NLC to actively target lung cancer cells, release anticancer drugs (paclitaxel/doxorubicin) after inhalation of the NLC to induce cancer cell death, and release siRNAs targeting MRP1 and BCL2 mRNAs to ameliorate resistance to the drugs, thus effectively inhibiting tumor growth and preventing adverse side effects on healthy organs.

Nanoemulsions (NEs)

Nanoemulsions(NEs) are biphasic dispersions of two immiscible liquids: water-in-oil (W/O) or oil-in-water (O/W) droplets stabilized by amphiphilic surfactants, with long-term kinetic and thermodynamic stability.[93] NEs have been recognized by the US FDA as safe drug carriers capable of dissolving large quantities of hydrophobic drugs within their lipophilic cores and reducing enzymatic degradation and hydrolysis of the loaded drugs to achieve sustained drug release.[94] In addition, its small size, typically averaging 20–200 nm in diameter, allows it to cross cellular barriers by diffusion, thus maintaining retention and deposition in lung tissue for extended periods of time, and has great potential in the treatment of lung diseases.[12]

Tea tree oil (TTO), a natural essential oil, has potent antimicrobial activity and is almost unlikely to develop antimicrobial resistance. However, allergic reactions, instability, and hydrophobicity limit its clinical application.[95] Li et al prepared an inhalable TTO nanoemulsion (nanoTTO) consisting of TTO/Cremophor EL/water with an average size of 12.5 nm. In vitro, the nanoTTO was able to significantly inhibit *Escherichia coli, Acinetobacter baumannii, Klebsiella pneumoniae, Staphylococcus aureus*, and *Candida albicans*. In a rat model of fungal pneumonia, inhaled nanoTTO directly reaches microbially infected lung tissue, exhibits superior antifungal activity to fluconazole, and inhibits leukocyte recruitment and pro-inflammatory mediators to attenuate lung injury. In a rat model of bacterial pneumonia, the efficacy of nanoTTO, although slightly lower than that of penicillin, was achieved at a much lower dose and without significant adverse effects.[70] Due to the current prevalence of microbial bacterial resistance, inhaled nanoTTO are expected to be the alternative nanomedicine of choice for the treatment of bacterial and fungal pneumonia. Degradation and shedding of the glycocalyx, the gel-like layer that lines the surface of the lumen of the vascular endothelium, has been implicated as an important mechanism in the pathogenesis of acute lung injury.[96] El-Moslemany et al[71] prepared a tanshinone IIA-loaded NEs formulation (TSIIA-NE) using ultrasound technology based on bioactive natural ingredients, rhamnolipid biosurfactant and TTO (as the oily phase). TSIIA-NE ameliorated LPS-induced pulmonary ventilatory dysfunction and pathological changes through antioxidant (up-regulation of superoxide dismutase, glutathione peroxidase, down-regulation of malondialdehyde), anti-inflammatory (up-regulation of IL-10, down-regulation of TNF-α and IL-17) and inhibition of glycocalyx degradation, as evidenced by a 1.4-fold and 1.9-fold increase in tidal volume and minute respiratory volume, respectively, a 32% decrease in the wet/dry lung weight ratio, and an improvement in arterial blood gas levels.[71] Similarly, Arbain et al[72] prepared an O/W NE formulation loaded with quercetin using palm oil ester/ricinoleic acid as the oil phase. The formulation had an acceptable MMAD (3.09 ± 0.05 μm), high FPF (90.52 ± 0.10%), and percent inhaled (81.26 ± 1.28%), which met the physicochemical and nebulization characteristics required for deep lung delivery applications. In addition, NEs impart high stability to natural products and can continuously deliver quercetin and docetaxel to act on lung cancer tissue even under extreme environmental conditions, making them promising inhalable agents for the treatment of lung cancer.[72,73] In addition to demonstrating significant safety and bioaccumulation in lung tissue, NEs delivering naringin also accumulate in the brain, liver and bone, the major organs for lung cancer metastasis.[74] Moreover, natural products, due to their excellent anticancer activity and potential as chemotherapeutic sensitizers, make their combination with chemotherapeutic agents a potential combination for lung cancer treatment.[97] The synergistic effect of NEs-based formulations co-loaded with curcumin and docetaxel, which have good physicochemical and aerodynamic pulmonary delivery properties that can reduce docetaxel toxicity and improve bioavailability, will undoubtedly play an important role in the treatment of lung cancer.[75,76]

Polymeric Nanoparticles

Polymers are mainly classified as natural polymers (eg, chitosan nanoparticles) or synthetic polymers (eg, poly(lactic-co-glycolic acid, PLGA), which have good properties such as good biodegradability, biocompatibility, and controllable drug release profile. Drugs can be encapsulated within the polymer or coupled to the surface of the polymer, and further modification of the ligand on the surface allows for targeted delivery of the drug.[29,98] In nanoformulations for inhalation drug delivery, polymeric nanoparticles help prevent the drug from being cleared by lung macrophages and ciliary mucus mechanisms, and are able to remain in the lungs longer to exert their effects (Table 3).

Antibiotic resistance is one of the most serious medical problems today, and urgent clinical needs require the timely discovery of alternative therapies for bacterial infections. Curcumin, a natural bacterial inhibitor, was prepared into pure curcumin nanoparticles by evaporative precipitation of nanosuspensions, solid dispersions and antisolvent precipitation, which in turn kills bacteria deep in the alveoli via inhaler without using any support or nano-carrier.[8] PLGA nanoparticles co-loaded with antibiotics (tobramycin, ciprofloxacin or azithromycin), N-acetylcysteine and curcumin, resulting in a combination of antimicrobial, mucolytic and anti-inflammatory properties to improve antibiotic resistance for effective control of pulmonary infections.[99] Moreover, as a naturally occurring photosensitizer, curcumin-based antimicrobial photodynamic therapy offers new options for improving drug-resistant bacterial pneumonia.[109] Curcumin-loaded inhalable PLGA nanoparticles adhered tightly to the bacterial cell wall and stimulated antimicrobial phototoxicity under an applied low-energy light source, disrupted bacterial morphology and ultrastructure, and significantly inhibited the growth

Table 3 Natural Products-Based Inhaled Polymeric Nanoparticle Formulations for the Treatment of Pulmonary Diseases

Natural Products	Nanoformulation	Diseases	Size (nm)	Aerodynamic Diameter (μm)	Zeta Potential (mV)	Polydispersity Index (PDI)	Mechanism	Refs
Curcumin	Pure curcumin nanoparticles	Pulmonary infections	65.3/98.7/ 47.4	–	–	–	Killing bacteria lying deep down within the alveoli of lungs	[8]
	Antibiotics with N-acetylcysteine and curcumin-loaded PLGA-nanoparticles	Pulmonary infections	105 ± 1.5	2.16–2.63	−9.1 ± 4.6	0.063 ± 0.019	↓TNF-α, IL-8, and IL-1β	[99]
	Chitosan modified curcumin loaded PLGA nanoparticles	Pulmonary infections	187.17 ± 2.77	–	+6.47 ± 0.79	0.09 ± 0.03	↓Staphylococcus saprophyticus subsp. bovis and Escherichia coli DH5 alpha	[100]
	Curcumin-loaded PLGA-nanoparticles embedded in a mannitol matrix	Pulmonary infections	185.96 ± 16.79	2.88 ± 0.13	−4.71 ± 0.79	0.11 ± 0.04	↓Staphylococcus saprophyticus subsp. bovis and Escherichia coli DH5 alpha	[101]
Quercetin	Chitosan-assisted encapsulation of quercetin in nanoparticles	Silicosis	168.19 ± 2.07	–	30.15 ± 2.37	0.134 ± 0.011	↑Antioxidant and anti-inflammatory activities of quercetin	[102]
Resveratrol	Resveratrol-cyclodextrin complex loaded biodegradable nanoparticles	Non-small cell lung cancer	264.2 ± 0.03	2.2±0.4 μ	−1.46 ± 1.47	0.16 ± 0.03	↑Cellular uptake, cytotoxicity, apoptosis, and antioxidant activity	[103]
Paclitaxel	Reactive Oxygen Species/Glutathione-Responsive Paclitaxel Dimeric nanoparticles	Lung cancer	154.8 ± 1.7	–	–14.7 ± 0.1	0.111 ± 0.039	↑Drug release rate	[104]
Docetaxel	Cholesterol-PEG co-modified poly (n-butyl) cyanoacrylate nanoparticles	Lung cancer	182.3 ± 3.2	4.20 ± 0.12	−7.31 ± 0.46	0.217 ± 0.011	↑The pulmonary absorption time and pass through the air-blood barrier and enter the brain	[105]
Naringin	PLGA nanoparticles	Lung cancer	215 to 267	5.65 ± 0.18	−18.3 to −25.9	0.071 to 0.16	↑High distribution to the lung, bones, brain, and liver	[106]
Paclitaxel	Spray-dried chemotherapeutic PEGylated phospholipid particles	Lung cancer	–	3.4–7	–	–	↑Mucus penetration	[107]
	Biomimetic endogenous pulmonary surfactant phospholipid modified nanoparticles	–	221–234	–	−34 to −28	0.18–0.21	↑Mucoadhesive or mucus penetration properties	[108]

Notes: ↑, increase or promote; ↓, decrease or inhibit.

of *Staphylococcus saprophyticus* subsp. *bovis* (Gram-positive bacteria) and *Escherichia coli* DH5 alpha (Gram-positive bacteria).[100,101]

Silicosis, caused by excessive inhalation of dust containing crystalline silica, is a life-threatening disease of pulmonary fibrosis for which there is a lack of effective treatment.[110] The natural product quercetin may be an effective strategy against fibrosis due to its antioxidant and anti-inflammatory activities. Quercetin encapsulated in chitosan-assisted manufactured nanoparticles (Qu/CS-NPs) facilitated the enhancement of quercetin's antifibrotic activity by virtue of its excellent encapsulation ability, excellent hydrophilic stability, and outstanding controlled and slow release capabilities. Inhaled Qu/CS-NPs ameliorated silica-induced silicosis-associated fibrosis by reducing ROS and malondialdehyde production to attenuate oxidative stress, inhibiting IL-1β and TNF-α release to alleviate inflammation, and downregulating α-smooth muscle actin levels and inhibiting extracellular matrix deposition to improve lung histology.[102] Given the negligible toxicity, inhalation of nanomodified natural products may be a viable therapeutic option for the treatment of silicosis.

Resveratrol, a natural polyphenol found in fruits, has excellent anticancer activity and low toxicity; however, its low water solubility and instability limit its clinical use.[111] The loading of sulfobutylether-β-cyclodextrin onto PLGA polymers (CD-RES NPs) perfectly ameliorates the above-mentioned deficiencies of resveratrol, with a 66-fold increase in its water solubility. Moreover, the excellent aerodynamic properties of CD-RES NPs after inhalation endowed resveratrol with enhanced anticancer efficacy as evidenced by significantly increased cellular uptake, cytotoxicity, antioxidant and pro-apoptotic activities.[103] Notably, tumor cells typically possess higher levels of ROS and glutathione (GSH) compared with normal cells, resulting in greater redox potentials.[112] Based on this, Tian et al[104] designed ROS/GSH-responsive paclitaxel dimer nanoparticles, which were able to rapidly decompose in the ROS- and GSH-rich tumor microenvironment thereby increasing local paclitaxel exposure and accumulation, exhibiting enhanced anticancer potential and reduced systemic toxicity. Metastasis is also a major threat to the treatment and prognosis of lung cancer. Hu et al[105] designed Cholesterol-PEG Co-Modified Poly (n-Butyl) Cyanoacrylate Nanoparticles for sustained pulmonary delivery of docetaxel. The PEG modification could avoid docetaxel clearance by macrophages and prolong the lung uptake time. Cholesterol modification, on the other hand, promotes docetaxel diffusion across the blood-brain barrier and into the brain in a sustained release fashion, making it a promising and effective vehicle for the treatment of lung cancer brain metastases.[105] In addition, bone and liver are common metastatic sites of lung cancer. Inhalation of naringin-encapsulated PLGA nanoparticles can not only accumulate in lung tissue, but also exist in large quantities in bone, liver, and brain, which will undoubtedly be an effective therapeutic strategy to control lung cancer metastasis.[106]

Inhaled nanoparticles deliver chemotherapy drugs deeper into the lungs than traditional intravenous drug delivery due to their smaller size and more localized drug delivery, which could significantly improve the efficacy of drugs such as paclitaxel.[107] However, inhaled nanomedicines inevitably interact with surface-active substances in the lung, forming a "surfactant corona" that affects drug adhesion/penetration. Paclitaxel-loaded PLGA nanoparticles were modified with biomimetic endogenous lung surfactant phospholipids, such as phosphatidyl dipalmitoyl phosphatidylcholine. The different phospholipids conferred adhesion, mucus permeability and cellular uptake properties to the nanoparticles, respectively, and modulated their retention in bronchoalveolar lavage fluid, uptake by alveolar macrophages and uptake by lung tissues, providing a scientific rationale for improving the intrapulmonary distribution of inhaled formulations.[108]

Other Nanocarriers

Nanomicelles are thermodynamically stable systems composed of amphiphilic polymers with small particle size, strong adsorption capacity, good biocompatibility and targeting. The hydrophobic core can load insoluble drugs, which is an effective way to improve the oral absorption of insoluble drugs, while the hydrophilic shell can prevent the micelles from being recognized by the reticuloendothelial system, thus prolonging the circulation time of drugs in the body.[113,114] Micelle-based delivery systems can be prepared that are both tissue-targeted and biologically active, delivering natural products to the deep lung for enhanced pharmacological activity.[114,115] Mahajan et al[116] prepared curcumin-loaded polymeric micelles based on l-lactide grafted xyloglucan and then used freeze-drying technique to prepare DPI formulations for pulmonary delivery of curcumin. The local concentration of curcumin was higher in deep lung tissues and was maintained at the effective drug concentration for a longer period of time. Matrix metalloproteinases (MMPs),

specific markers of malignancy, are involved in malignant behaviors such as angiogenesis, invasion and metastasis in lung cancer.[117] MMP2/9-triggered release micelles were developed for pulmonary delivery of paclitaxel. Upon nebulized inhalation, paclitaxel was released in a concentration-dependent MMP2/9-triggered release at the tumor site and was rapidly taken up by cancer cells to enhance anticancer activity and reduce toxicity to healthy lung cells.[118]

Nanogels are non-toxic and biocompatible porous carriers with large surface area and drug loading capacity, making them particularly suitable for clinical topical applications.[119] For example, cholesteryl group-modified pullulan self-assembled polysaccharide nanogels for cancer vaccine delivery and enhancement of immune response against tumor cells.[120] Chen et al[121] designed an inhalable nanogel with a "material-drug" structure to improve the low solubility and bioavailability deficiencies of quercetin, a natural flavonoid with excellent antioxidant and anti-inflammatory properties. In this nanoformulation, quercetin and alginate are cross-linked by Ca^{2+} and stabilized by intermolecular hydrogen bonding, resulting in a "co-construct" water-soluble nanogel (QU-nanogel). In a rat model of acute lung injury, inhaled QU-nanogel provided targeted delivery of quercetin to the lung, attenuated lung inflammation and oxidative damage, and prevented subsequent lung fibrosis as evidenced by down-regulation of inflammatory cytokines (TNF-α, IL-6, and IL-1β) and up-regulation of antioxidant enzymes (SOD, catalase, and heme oxygenase-1).[121]

Exosomes, which are small lipid bilayer nanoparticles derived from many cell types, can deliver drugs to specific cell types or tissues for targeted drug delivery due to their stable structure and unique permeability.[122] Zheng et al[123] encapsulated paclitaxel using T cell-derived exosomes expressing chimeric antigen receptors (PTX@CAR-Exos). In a mouse model of orthotopic lung cancer, inhaled PTX@CAR-Exos accumulated in the tumor region by targeting the mesothelin-expressing Lewis lung cancer through the anti-mesothelin single-chain variable fragment of CAR-Exos, thereby reducing tumor volume and prolonging survival of the mice. In addition, PTX@CAR-Exos reprogrammed the tumor microenvironment and reversed the immunosuppression, as evidenced by CD8 T-cell infiltration and increased levels of IFN-γ and TNF-α.[123]

Nanocochleates, a new type of nanocarrier with a helical structure composed of soluble lipid molecules, have been prepared as oral formulations to improve the bioavailability of chemotherapeutic drugs such as paclitaxel.[124] The surface activity of nanocochleates was found to be similar to that of endogenous lung surfactant, which is expected to be used as both a drug delivery vehicle and lung surfactant for lung diseases. Paclitaxel-loaded nanocochleates (PTX-CPTs) exhibited excellent lung surface activity and terminal airway patency. Inhaled PTX-CPTs were readily deposited in the deep alveoli, which in turn enhanced cellular uptake-mediated cytotoxicity via energy-dependent endocytosis. In a mouse model of melanoma lung metastasis, PTX-CPTs significantly inhibited the numbers of tumor nodules and percent metastasis area covered by melanoma cells in the lung, and reduced respiratory complications and side effects of chemotherapeutic agents.[125]

In addition, albumin nanoparticles,[126,127] nano transfersome,[128] and nanocapsules[129] have been prepared to deliver natural compounds to the lungs as inhalable nanoformulations. Moreover, the preparation of natural phytochemicals into nanocrystals for pulmonary delivery using methods such as milling can also improve the bioavailability of natural phytochemicals[130,131] (Table 4).

Microparticles

Microparticles have excellent aerodynamic properties with an average size of about 5 μm, and spray drying produces inhalable formulations that effectively evade phagocytosis by alveolar macrophages and penetrate deep into the lungs.-[132,133] Using materials such as PLGA, alginate, chitosan and lipids, they can be easily atomized as dry powder formulations for sustained drug release in the lungs (Table 5).

Salvianolic acid B (Sal B), a water-soluble component of *Salvia miltiorrhiza* Bunge, prevents or delays the onset and progression of idiopathic pulmonary fibrosis by modulating inflammatory cytokines and fibrosis-related cytokines. Its preparation as an inhalable dry powder formulation may overcome the limitations of oral and intravenous administration.[134,135] Sal B-DPI was prepared by spray-drying using L-leucine as an excipient for targeted delivery to the deep lung as a dry powder.[134] Similarly, Jiang et al[135] prepared new Sal B powder formulations containing L-arginine and lecithin using ball milling technique. L-arginine was used to modulate the strong acidity of Sal B solution, and lecithin could improve the flowability and biocompatibility due to its similarity in composition to lung surfactants. These

Table 4 Natural Products-Based Other Inhaled Nanocarriers for the Treatment of Pulmonary Diseases

Nanocarrier	Natural Products	Nanoformulation	Diseases	Size (nm)	Aerodynamic Diameter (μm)	Zeta Potential (mV)	Polydispersity Index (PDI)	Mechanism	Refs
Micelles	Paclitaxel	Spray-dried inhalable powders containing polymeric micelles	Lung cancer	102 to 196	3.8 ± 0.98	−9.4 to −13.8	-	↑Cytotoxic activity of PTX	[115]
	Curcumin	Curcumin loaded polymeric micelle based on a newly synthesized grafted xyloglucan	Lung cancer	102.4	106.67 nm	−18.2	0.275	↑Bioavailability	[116]
	Paclitaxel	Matrix metalloproteinase 2/9-triggered-release	Lung cancer	34.43±0.47	–	–	0.35±0.01	↑Tumor sensitivity to chemotherapeutics ↓The toxicity of chemotherapy to healthy lung cells	[118]
Nanogel	Quercetin	Quercetin -alginate nanogel	Acute lung injury	61.87	–	− 30	–	↓Pulmonary inflammation and oxidative stress damage	[121]
Exosomes	Paclitaxel	Paclitaxel loaded CAR-T cell-derived exosomes	Lung cancer	100	–	−17.3	−25.7	↓Tumor size; ↑Survival with little toxicity; Reprogramming the tumor microenvironment and reversing immunosuppression.	[123]
Nanocochleates	Paclitaxel	Paclitaxel-carrying aerosol nanocochleates	Lung cancer	384.8 ± 96.6	–	−23.5 ± 1.9	0.12 ± 0.08	↓Tumor growth	[125]
Albumin nanoparticles	Apigenin	Apigenin-Loaded Albumin Nanocarriers	Pulmonary inflammation	376 ± 7.824	2.123 ± 0.098	−19.20 ± 0.818	0.285 ± 0.01	↑Antioxidant activity.	[126]
	Silymarin/ curcumin	Silymarin/curcumin loaded albumin nanoparticles	COVID-19	–	–	32 ± 2	–	↑Anti-viral/inflammation activity	[127]
Transfersome	Paclitaxel	Paclitaxel-loaded micro or nano transfersome formulation	Lung cancer	292.16 to 483.62	–	−2.61 to −2.55	0.434 to 0.451	↑Toxicity to cancer cells while safe to normal lung fibroblast cells	[128]
Nanocapsules	Paclitaxel	Paclitaxel in lipid nanocapsules	–	53.4 ± 1.9	2.7 ± 0.1	−5.84 ± 0.87	0.08 ± 0.02	–	[129]
Nanocrystals	Baicalein	Baicalein nanocrystal	–	335±18	–	–	0.12	↑The solubility and lung absorption rate of baicalein	[130]
	Curcumin	Curcumin nanocrystals	–	10 to 40	–	–	–	↑The blood concentration and lung deposition of curcumin	[131]

Notes: ↑, increase or promote; ↓, decrease or inhibit.

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Table 5 Natural Products-Based Inhaled Microparticles for the Treatment of Pulmonary Diseases

Natural Products	Inhalable Formulations	Diseases	Size (μm)	Mechanism	Refs
Quercetin	Quercetin solid lipid microparticles	Lung cancer	2.90 ± 0.30	↑Quercetin diffusion	[132]
	Quercetin-loaded lipid microparticles prepared with tristearin and hydrogenated phosphatidylcholine		4.1±0.2	↑stability and cellular uptake of quercetin	[133]
Salvianolic acid B	Salvianolic acid B dry powder inhaler	Idiopathic pulmonary fibrosis	1.00–1.17	↓Inflammatory factors and fibrotic cytokines	[134]
	Salvianolic acid B powder formulation containing L-arginine and 2% of lecithin		1.83 ± 0.18	↑Drug concentration in the lung and the bioavailability	[135]
Baicalin	Baicalin/ambroxol hydrochloride combined dry powder inhalation formulation		1.24 −2.01	↓Inflammatory factors and pulmonary fibrosis ↑IFN-γ	[136]
Fisetin	Dry powder sulfobutylether-β-cyclodextrin complex for pulmonary delivery of fisetin	Lung cancer	1.48 ± 0.08	↑Aqueous solubility of fisetin	[137]
Paclitaxel and Curcumin	Dry powder inhalation formulation containing paclitaxel and a curcumin		2.64–3.12	↑Apoptosis/necrotic cell death and G2/M cell cycle arrests	[138]
Resveratrol	Resveratrol spray-dried formulation	Chronic obstructive pulmonary disease	3.7 ± 0.1	↓IL-8, TNF-α, LPS, and TGF-β1	[139]
	Co-spray dried resveratrol and budesonide inhalation formulation		1.2 to 6.23	↓Inflammation and oxidative stress	[140]
Naringin	Naringin microparticles prepared by spray-drying using water/ethanol (6:4) co-solvents	–	1.17–9.47	↑Solubility and improved aerodynamic behaviour.	[141]
	Naringin microparticles prepared by spray-drying a solution containing 5% leucine in a co-solvent of ethanol and water (3:7).	Cystic fibrosis	2.75–3.42	↓NF-κB and MAPK/ERK pathways	[142]

Notes: ↑, increase or promote; ↓, decrease or inhibit.

two dry powder formulations have good powder properties, low irritation, effective pulmonary delivery, high bioavailability and pulmonary drug concentration. By attenuating oxidative damage and modulating inflammatory factors and fibrotic cytokines (eg, I/III Collagen type α1, intercellular adhesive molecule-1, fibronectin, inducible nitric oxide synthase, and arginase type 1) during disease progression, Sal B-DPI significantly alleviated bleomycin-induced pulmonary fibrosis as evidenced by the reduction of alveolar wall congestion, inflammatory cell infiltration, emphysema extent, and lung ventilatory function.[134,135] Moreover, the DPI co-loaded with baicalein/ambroxol hydrochloride demonstrated antifibrotic, anti-inflammatory, and antioxidant effects of pirfenidone due to its pulmonary targeting, rapid onset of action and high pulmonary bioavailability.[136] These inhaled formulations will undoubtedly help to address the current dilemma of the extreme shortage of drugs for the treatment of pulmonary fibrosis.

Complexation of the natural flavonoid fisetin with sulfobutylether-β-cyclodextrin increased the solubility of fisetin while maintaining its antioxidant activity. Subsequently, it was fabricated into a low-density inhalable powder using a spray-drying method for delivery to deep lung tissues for therapeutic purposes.[137] However, the dose of fisetin required for this formulation to achieve a significant degree of anticancer activity is relatively high, and thus co-delivery of natural products and chemotherapeutic agents to the particles may achieve superior efficacy. Curcumin and paclitaxel were homogeneously mixed and co-jet milled to form particles suitable for inhalation with a MMAD of 2.64–3.12 μm. This co-delivery regimen possessed, on the one hand, enhanced anticancer activity, inducing apoptosis/necrotic cell death, G2/M cell cycle arrests and oxidative stress (increase in ROS, mitochondrial depolarization and decrease in ATP content). On the other hand, the presence of curcumin attenuated the toxic effects of paclitaxel on healthy cells.[138] This suggests that combination formulations of chemotherapeutic agents with chemoprotective agents (natural products) are a promising option.

Inhaled medications are already the first-line treatment for COPD, such as budesonide, but some airway inflammation is resistant to glucocorticoids, leading to treatment failure. Inhalable dry powder formulations of resveratrol with an MMAD of 3.7 ± 0.1 μm were prepared using a spray-drying method, showing excellent lung deposition, transport and cellular uptake, which in turn inhibited the production of multiple inflammatory mediators (eg, IL-8, TNF-α, and TGF-β1) is expected to be efficacious in inflammatory lung diseases such as COPD.[139] In addition, the combination of resveratrol and budesonide to design inhalable microparticles holds promise for synergistic efficacy in the treatment of COPD. Budesonide reduced cohesion between resveratrol particles and reduced particle agglomeration, resulting in significantly improved aerosol properties suitable for inhaled drug delivery, which in turn synergistically inhibited alveolar macrophage inflammation and oxidative stress.[140] Naringin is also a flavonoid with excellent antioxidant activity, and inhalable naringin microparticles were prepared by spray-drying method with higher solubility, lower density and improved aerodynamic properties.[141] Next, the researchers used leucine to further enhance the aerosol properties of naringenin microparticles, which in turn enhanced the pharmacological activity of naringenin, inhibiting NF-κB and MAPK/ERK pathways to attenuate the hyperinflammatory state associated with cystic fibrosis.[142]

Nanocomposites and Nanoaggregates

Although nanocarriers are excellent carriers for targeted drug delivery, their size range (<1 μm) makes them easily exhaled before reaching the target. In general, particles in the size range of 1–5 μm can only be deposited at the lung base and reach the alveoli, thus fully utilizing the anti-cancer activity of the drug.[143] Physical instability and low lung deposition efficiency of nanoparticles, particle-particle interactions also hinder drug delivery to the lungs. Despite overcoming this challenge, microparticles undergo pulmonary clearance via alveolar macrophages.[12] Incorporating nanoparticles into inhalable micron-sized carriers combines the advantages of both micron and nanoparticle drug delivery systems and will likely offer unique advantages in pulmonary drug delivery,[144] thus taking full advantage of natural products (Table 6).

Ahmed et al[145] first prepared resveratrol-loaded bovine serum albumin nanoparticles (BSA NPs), and then the NPs were co-spray-dried into composite microparticles with different carriers including mannitol, dextran, trehalose, leucine, glycine, aspartic acid, and glutamic acid. Encouragingly, the MMAD of these microparticles was less than 5 μm, and all were suitable for deep lung deposition, especially leucine aerosolization was the most effective with an FPF of 75.74%. The composite microparticles released NPs upon contact with lung fluid and sustained the release of resveratrol, which successfully ameliorated bleomycin-induced pulmonary fibrosis in mice.[145] Similarly, other natural products, such as curcumin[146,147] and honokiol,[148] could be prepared first as nanoparticles to enhance their therapeutic effects, followed by

Table 6 Natural Products-Based Inhaled Nanocomposites and Nanoaggregates for the Treatment of Pulmonary Diseases

Natural Products	Nanoformulation	Diseases	Nanoparticle Size (nm)	Nanocomposites/ Nanoaggregates Size (μm)	Aerodynamic Diameters (μm)	Mechanism	Refs
Curcumin	Curcumin-loaded PLGA nanoparticles with chitosan-grafted-PEG or chitosan	–	243.4±34.8	1.09 ± 0.02 to 1.80 ± 0.01	1.25–1.96	↑Efficient deposition in the airways	[143]
Resveratrol	Resveratrol-loaded spray-dried composite microparticles	Idiopathic pulmonary fibrosis	177.67 ± 0.95	2.64 ± 1.57	2.28 ± 0.22	↓Hydroxyproline, TNF-α, and matrix metalloproteinase-9	[145]
Curcumin	Curcumin loaded Nano-in-Microparticles	Lung cancer	181.20±11.52	0.5–4	3.02 ± 0.07	↑Sufficient deposition in the lung	[146]
	Curcumin nanocomposite particles	Lung cancer	135	2.1	1–3	↑Sufficient deposition in the lung	[147]
Honokiol	Honokiol-loaded chitosan microparticles	–	–	6.9–8.4	2.8–3.3	↑Sufficient deposition in the lung	[148]
Paclitaxel/ quercetin	Nanoparticles in the form of polymeric microspheres loaded with paclitaxel and quercetin	Lung cancer	100	3.373	1.804±0.022	↑Circulation time and a markedly high accumulation in the lung	[149]
Quercetin and paclitaxel	Nanocomposite microparticles modified by cetuximab and loaded quercetin and paclitaxel	Non-small cell lung cancer	–	4.54 ± 0.30	2.91 ± 1.94	↑The accuracy targeting ability and killing effect	[150]

Notes: ↑, increase or promote; ↓, decrease or inhibit.

the use of chitosan as a material for encapsulating the nanoparticles and spray-drying to produce composite microparticles with appropriate aerodynamic properties to disintegrate into pristine nanoparticles to exert their medicinal effects when sufficiently deposited and redispersed in the lungs.

Inhalable nano-formulations with deformable size also contribute to lung retention and targeted drug accumulation.[81] El-Sherbiny et al[143] doped curcumin-loaded PLGA nanoparticles into amphiphilic PEG-chitosan copolymer hydrogel microspheres to develop swellable biocompatible microparticles. Upon inhalation, the formulation was able to rapidly expand under humid conditions, such as in the lung, and evade macrophage uptake, allowing for effective deposition in the airways and controlled release of curcumin over 24 hours.[143]

In addition, composite particles provide an optional option for drug co-loading. Liu et al[149] prepared NPs loaded with paclitaxel and quercetin as polymeric microspheres (PMs). PMs are polymers formed from a large number of NPs with a uniform size ranging from 1 to 5 μm in diameter. PMs are inhaled deep into the lungs and redispersed into NPs with diameters ranging from 250 to 350 nm. This formulation prolongs drug release and increases the retention time of paclitaxel in the lungs. Quercetin inhibits the expression of the P-glycoprotein drug efflux pumps, which in turn improves the body's sensitivity to paclitaxel.[34] Cui et al[150] fabricated cetuximab-modified nanoparticles loaded with paclitaxel and quercetin, respectively, and then used a spray-drying technique to composite these two nanoparticles into nanocomposite microparticles (P/Q@CNMPs). The P/Q@CNMPs had a suitable aerodynamic diameter and homogeneous morphology to meet the requirements for particle deposition in the lungs. The excipient mannitol, which is highly absorbent and easily disintegrated, ensures rapid decomposition of the nanocomposite microparticles in the moist environment of lung mucus and lung surface active substances to release drug-loaded nanoparticles. Cetuximab modification enhances the precise targeting and killing effect of the formulation on the surface high-expression EGFR lung cancer cells.[150] These results show that nanocomposites and nanoaggregates combine the advantages of both nano- and micro-size particles and have great potential for targeted drug delivery in lung diseases.

Conclusion and Prospects

Although inhalable nanoformulations are still in the exploratory stage, it is clear that the direct, inhalable route is more favorable for pulmonary drug delivery and lung disease control than conventional systemic delivery, significantly avoiding drug loss, off-target effects, systemic and organ toxicity. The real clinical use of inhaled formulations currently faces a number of challenges: the first is to design a drug delivery system that matches the physiological-pathological characteristics of the lung. The size, surface properties, and aerodynamic characteristics of micro/nano carriers determine their ability to target deeper regions of the lung (alveoli) while safely crossing the mucosal barrier to avoid clearance by pulmonary macrophages. The second is potential toxicity. The drug delivery system itself may be potentially toxic, and the cumulative effect of prolonged use without timely pulmonary clearance may have unknown consequences, which is certainly contrary to the intended purpose. Even more critical is the return to nature. Medicinal plants are a promising source for inhalation formulations. More and more researchers and drug development companies should consider natural plant components when designing and developing novel dosage forms. How to optimize the bioavailability of natural products based on the full pharmacological activity of botanical ingredients is a current problem that needs to be solved. It can be expected that, along with the advances in nanomaterials and inhaled drug delivery technology, more and more new inhaled formulations will eventually be used in various lung diseases to change the current dilemma of lung disease prevention and control.

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