JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2024, VOL 7, NO S10

Innovations in Respiratory Therapy: Addressing Pulmonary Fibrosis with Inhalation Techniques

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Abstract

Pulmonary fibrosis (PF) is a debilitating condition with increasing incidence worldwide. Idiopathic pulmonary fibrosis (IPF) is the most common form of PF, characterized by progressive lung scarring and declining lung function. Current oral treatments, such as pirfenidone and nintedanib, have limitations in efficacy, cost, and adverse effects. Inhalation therapy offers a promising alternative by delivering drugs directly to the lungs, reducing systemic side effects and enhancing therapeutic efficiency. This review explores the advantages, challenges, and novel formulations of inhalation therapy for PF. Inhalation devices, including nebulizers, pressurized metered-dose inhalers, and dry powder inhalers, enable targeted drug delivery. However, optimizing particle size, overcoming biological barriers, and mitigating immune responses remain challenges. Novel inhalation formulations, such as agonists/inhibitors of key pathways, nano-sized drug systems, and nanocarrier delivery systems, have shown promising results in preclinical studies. Polymeric nanoparticles, lipid-based nanocarriers, and gene therapy approaches demonstrate enhanced lung deposition, prolonged retention, and improved therapeutic outcomes. Other innovative interventions, such as inhaled gases and extracellular vesicles, also exhibit

potential. While further research is needed to translate these findings into clinical practice, inhalation therapy represents a promising frontier in the management of PF, offering hope for improved patient outcomes and quality of life.

Keywords: Respiratory Therapy, Pulmonary Fibrosis, Inhalation therapy

Introduction

Pulmonary fibrosis (PF) poses a significant threat to human health and quality of life. The incidence of idiopathic pulmonary fibrosis (IPF) has risen markedly, with rates ranging between 8 and 60 cases per 100,000 individuals (Duchemann et al., 2017). Additionally, pneumoconiosis and cystic pulmonary fibrosis (CPF) impact hundreds of thousands of individuals globally (Shi et al., 2020). PF serves as a common feature of various conditions, including fibrous interstitial lung disease (ILD), pneumoconiosis, and CPF, with IPF contributing to the majority of ILD cases. Numerous pulmonary conditions, such as chronic obstructive pulmonary disease (COPD), acute or chronic lung injuries, and lung injuries induced by radiation or immune checkpoint inhibitors, can lead to PF.

Patients with PF typically present with clinical symptoms such as chronic cough, sputum production, and progressive dyspnea. For phenotypes classified as progressive pulmonary fibrosis (PPF), it is critical to provide effective and safe treatment strategies aimed at prolonging life expectancy. Guidelines from the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) recommend pirfenidone (PFD) and nintedanib as oral treatments for mild-to-moderate IPF. Although the precise mechanism of action of PFD remains unclear, evidence supports the efficacy of both drugs in mitigating the decline of forced vital capacity (FVC) (Richeldi et al., 2014). However, the available data are insufficient to confirm whether these drugs reduce acute IPF exacerbations, decrease mortality, or are applicable for non-IPF PPF. Moreover, their high cost presents a barrier to widespread clinical use. In addition to pharmacological therapies, guidelines also endorse non-pharmacological interventions such as oxygen supplementation and pulmonary rehabilitation. Lung transplantation remains a feasible treatment for IPF patients; however, absolute and relative contraindications, coupled with a severe donor shortage, limit its widespread implementation. PF is characterized by a pathological process of lung tissue damage and repair, encompassing chronic inflammation, oxidative stress, immune activation, and altered fatty acid metabolism (Otoupalova et al., 2020). While fibroblast activity and extracellular matrix (ECM) deposition represent protective responses to tissue injury, the progression of PF is heterogeneous and often irreversible. Its underlying pathological mechanisms involve numerous factors, including genetic and epigenetic modulation, infections, smoking, occupational or environmental pollutants, chemoradiotherapy, reflux/microaspiration, and certain drugs such as bleomycin (BLM) and amiodarone.

The pathological process of PF involves phenotypic cellular transformations and activation of signaling pathways. Epithelial dysfunction is a pivotal aspect, as damage to alveolar epithelial cells (AECs) triggers pathological remodeling of the alveolar epithelium. Alveolar type II epithelial cells (AT2), the primary progenitor cells of the epithelium, secrete surfactant protein C (SP-C) and play a critical role in maintaining alveolar homeostasis. A study utilizing single-cell sequencing of epithelial cells from IPF patients identified significant enrichment of pathological epithelial cell populations that promote ECM deposition, reinforcing the notion of repetitive epithelial injury (Habermann et al., 2020). The ECM deposition phase, driven by fibroblast and myofibroblast activation, represents the central stage of PF. Environmental triggers interacting with genetic predispositions can result in disordered or excessive ECM deposition in the lungs. This feedback loop of fibroblast activity and ECM deposition

perpetuates fibrosis, leading to lung remodeling, increased tissue stiffness, and dyspnea (Freeberg et al., 2021). The pathogenesis of IPF encompasses numerous pathological processes, including DNA damage, transforming growth factor-beta (TGF-β) signaling, oxidative stress, inflammatory stimuli, and ECM deposition. These mechanisms interact and collectively contribute to IPF progression. The TGF-β pathway plays a central role, as it promotes ECM production via downstream effectors like phosphorylated SMAD 2/3 proteins, which regulate gene expression associated with fibrosis. The TGF-β system also activates the hedgehog signaling pathway and integrin alpha-v beta-6 (αvβ6) protein, further exacerbating PF. Additionally, oxidative stress and inflammation-related pathways significantly influence PF pathogenesis. Reactive oxygen species (ROS), primarily generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase family members such as NOX4, are produced in the mitochondria following TGF-β receptor binding. This binding enhances TGF-β gene expression through pathways like nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1), Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3), and p38 mitogen-activated protein kinase/nuclear factor kappa-light-chain-enhancer of activated B cells (p38 MAPK/NF-κB), promoting collagen deposition and aggravating PF progression. These intricate molecular mechanisms, illustrated in Fig. 1(i) and (ii), underscore the complexity of PF pathogenesis.

Emerging therapeutic strategies, particularly novel inhalation therapies, have shown promise in managing PF. Inhalation therapy, already well-established in COPD and asthma management, offers potential for PF treatment. Advances in nanoplatform technology have enhanced inhalation therapy, particularly through innovations in microparticles (MPs) and nanoparticles (NPs). These include nano-sized drug systems and nano-carrier drug delivery systems. Specific inhibitors or agonists targeting relevant signaling pathways, as well as exosomes and other innovative drugs, benefit from these advancements.

Despite progress in understanding PF, its clinical management remains suboptimal. However, novel inhalation therapeutic techniques offer new opportunities and challenges that warrant further exploration. This review provides an overview of the benefits and limitations of inhalation therapy, classifications of inhalation methods, and applications of emerging inhalation techniques in PF treatment. Such insights aim to advance the field and improve clinical outcomes for PF.

Classification of Inhalation Therapy

Inhalation therapy converts therapeutic agents into aerosols, utilizing various devices such as nebulizers, pressure metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft mist inhalers. Each device presents unique advantages and limitations, making them suitable for specific therapeutic contexts (Laube et al., 2011).

Nebulization

Nebulization involves converting drugs dissolved in liquids (solutions or suspensions) into a fine mist for inhalation through nebulizers, a method with a long-standing history in medical applications. Nebulizers are particularly suited for patients who struggle with other inhalation devices, such as children, elderly individuals, or those with severe respiratory conditions. The evolution of nebulizer technology has seen the introduction of air-jet nebulizers, ultrasonic nebulizers, mesh nebulizers, and vibrating mesh nebulizers (VMNs) in sequential order.

The properties of aerosols generated during nebulization are influenced by several factors, necessitating careful consideration of device and drug formulation. Air-jet nebulization, for example, decreases the solution temperature (from 24°C to 17°C) due to solvent evaporation, resulting in very small droplets. In contrast, ultrasonic nebulization increases the liquid temperature due to ultrasonic vibrations, which reduce drug concentration, viscosity, and surface tension, facilitating smaller droplet formation. However, the size distribution of droplets varies depending on nebulization time, with air-jet nebulization showing an initial

increase in droplet size within the first 2 minutes before decreasing, while ultrasonic nebulization exhibits a decrease in droplet size during the first 4 minutes, followed by fluctuations over subsequent time intervals. These temperature changes affect aerosol surface tension, concentration, viscosity, and particle size, emphasizing the importance of considering both drug formulation and nebulizer characteristics when choosing a device.

Mesh nebulizers represent a significant advancement, combining the benefits of compression and ultrasonic nebulizers. Utilizing ultrasonic vibrations and a mesh nozzle design, they spray liquid through nozzle orifices. These devices offer advantages such as reduced noise, portability, higher lung deposition rates, minimal drug residuals, and enhanced stability. For example, Lin et al. demonstrated that VMNs consistently delivered salbutamol effectively over 28 days of use without cleaning, underscoring their stability (Lin et al., 2020). VMNs reliably produce homogenous aerosol particles (1–5 μm) for optimal lung deposition and single-use applications, reducing cross-infection risks. Mesh nebulizers have been found particularly effective for inhaled antibiotics in CPF treatment. However, VMNs are sensitive to the liquid's physicochemical properties and the atomization mechanism, especially with viscous liquids. Thus, both liquid properties and nebulization mechanisms should be considered when selecting nebulizers for inhaled antibiotics.

Despite their advantages, nebulizers have limitations. Drug wastage during nebulization is significant, with higher therapeutic doses required compared to devices like pMDIs and DPIs. Among nebulizers, VMNs exhibit the least drug loss, while air-jet nebulizers show the most. For instance, the nebulized dose of salbutamol sulfate solution is 5 mg/dose, whereas the aerosolized dose in pMDI is approximately 200 μg/dose for long-term use. Additionally, inadequate cleaning and disinfection of home nebulizers may lead to bacterial dispersion, posing risks to patients. Harris et al. observed bacteria dispersion from nebulizers inoculated with pathogens from CPF patients during salbutamol re-nebulization under high humidity (Harris et al., 2022). Many patients and caregivers remain unaware of proper cleaning practices or fail to disinfect nebulizers adequately (Murray et al., 2019). Hence, selecting an effective, safe, portable, stable, and cost-efficient nebulizer is crucial, coupled with educating patients and their families on proper maintenance to ensure effective treatment.

Pressurized Metered-Dose Inhaler (pMDI) and Dry Powder Inhaler (DPI)

Pressurized metered-dose inhalers (pMDIs) have been utilized for decades, functioning by using external pressure to release a solution or suspension from a sealed container. A shift from chlorofluorocarbon (CFC) to hydrofluoroalkane propellants has enhanced their performance by reducing spray velocity and producing smaller aerosols for improved lung deposition.

Dry powder inhalers (DPIs), introduced in the 1980s, are widely used in inhalation therapy and can be categorized into single-dose capsules, multi-dose reservoirs, and vesicle devices. These devices rely on inspiratory flow rates, peak inspiratory flow rates (PIFR), and device resistance to depolymerize drugs. PIFR is significantly associated with drug depolymerization and lung deposition rates. While DPIs require patients to initiate deep and forceful inhalation, which can be challenging for individuals with compromised lung function, studies suggest that patients with conditions like COPD, asthma, and CPF can often achieve the necessary inspiratory flow rates (Haughney et al., 2021).

Both pMDIs and DPIs share limitations, including relatively low pulmonary deposition rates, ranging between 20–40%, though pMDIs equipped with co-suspension technology can achieve rates up to 48%. This indicates that a substantial portion of the drug does not reach the target site. Proper inhalation technique and adherence are essential to maintain therapeutic efficacy, necessitating regular patient follow-ups and technique assessments. While pMDIs and DPIs are effective for respiratory conditions such as COPD and asthma, their specific limitations and

patient suitability must be considered. Educating patients and ensuring regular follow-ups are critical to achieving optimal outcomes.

Advantages and Challenges of Inhalation Therapy

Advantages

Inhalation therapy delivers drugs directly to the disease site thereby reducing systemic side effects commonly associated with oral or intravenous drug administration. The respiratory tract's direct connection to the external environment and the lungs' role in ventilation and gas exchange make inhalation therapy particularly effective for respiratory disorders. Systemic side effects often limit the use of drugs, such as the photosensitivity associated with pirfenidone (PFD) or diarrhea caused by nintedanib (Flaherty et al., 2019). By enabling localized treatment, inhalation therapy minimizes unnecessary systemic effects, making it an attractive option.

Inhalation Therapy in Respiratory Diseases: Mechanisms, Advantages, and Challenges

Mechanisms and Advantages

Inhalation therapy has been a cornerstone in managing chronic respiratory diseases like asthma and COPD due to its ability to deliver rapid clinical responses and provide immediate disease control. Inhaled bronchodilators and glucocorticoids are pivotal in this treatment approach, largely owing to their interaction with cellular receptors within the airways. For instance, β2 agonists and cholinergic receptor antagonists specifically target autonomic receptors on airway smooth muscles, highlighting the complexity and abundance of such receptors. Moreover, advancements in research have identified novel receptor targets for therapeutic intervention in pulmonary fibrosis (PF).

One of the key benefits of inhalation therapy is its capacity to enhance drug utilization by bypassing hepatic first-pass metabolism and mitigating gastrointestinal absorption issues. The pulmonary delivery of aerosols is noninvasive and achieves therapeutic effects with significantly lower doses compared to oral or intravenous routes, adhering to the principles of bioequivalence. Inhaled corticosteroids (ICS), such as budesonide and fluticasone propionate, exemplify this advantage with their high lung deposition rates, optimized residence time in the lungs, rapid systemic clearance, and minimal adverse effects. For idiopathic pulmonary fibrosis (IPF), pirfenidone (PFD), traditionally an oral treatment, has demonstrated promising results when nebulized. For instance, Rasooli et al. found that nebulized PFD administered over 14 days effectively mitigated paraquat-induced PF in rats, reducing the required dosage by nearly tenfold. Similarly, inhalation therapy with nintedanib has shown comparable therapeutic potential (Surber et al., 2020).

Inhalation therapy offers notable convenience, particularly for patients who struggle with swallowing oral medications or require frequent dosing. Portable inhalers enable flexible and accessible use, improving patient adherence. Additionally, this mode of therapy is customizable, with diverse devices and formulations designed to optimize drug delivery to individual needs.

Overall, inhalation therapy stands out for its targeted treatment, rapid response, enhanced drug efficiency, and patient convenience. With continuous innovation in inhalable drugs and delivery systems, its efficacy and applications in respiratory diseases are expected to grow.

Challenges in Inhalation Therapy

One significant challenge in inhalation therapy is optimizing drug deposition in the lungs, which depends on the aerosol's physicochemical properties. Particle size plays a crucial role, with deposition in the respiratory airways being most effective for aerosols with aerodynamic diameters under 5 μm in adults and under 3 μm in children. The mechanisms governing deposition patterns—such as inertial impaction, gravitational sedimentation, and Brownian motion—are influenced by particle size and flow dynamics. Larger particles (>1 μm) often experience inertial impaction at high flow rates, limiting delivery to the lower airways. Conversely, smaller particles (<0.5 μm) are more likely to be exhaled, reducing effective lung

deposition. Chronic lung diseases further exacerbate these challenges by altering deposition rates, as PF, for instance, decreases the efficiency of aerosol delivery to the lower airways due to airway alterations and reduced kinetic diameter of inhaled particles (Qin et al., 2022).

Biological barriers present another significant hurdle. Lung diseases like IPF and chronic pulmonary fibrosis (CPF) disrupt these barriers, compounding the existing physiological barriers of the lungs. The gas-blood barrier (GBA), which facilitates ventilation and prevents the entry of foreign particles, consists of multiple layers, including pulmonary surfactants, alveolar epithelial cells, matrix structures, and capillary endothelium. Pulmonary surfactant, secreted by alveolar type 2 (AT2) cells, is vital for maintaining alveolar stability and expelling foreign particles, but its effective utilization as a drug carrier remains a challenge. Pathological changes in IPF, such as repeated epithelial injuries and disrupted extracellular matrix (ECM) layers, further hinder drug penetration through the GBA. Similarly, in CPF, mutations in the CFTR gene impede mucus clearance, resulting in obstructed airways and limited drug transport.

Pulmonary Immune Responses and Drug Efficacy

The robust immune system of the lungs, comprising innate and adaptive immune cells, can present both opportunities and challenges for inhalation therapy. Innate immune cells, such as epithelial cells, macrophages, dendritic cells, and neutrophils, are responsible for detecting, phagocytosing, and clearing antigens. When antigens persist, adaptive immunity becomes active, with antigen-specific B and T cells neutralizing and clearing the pathogens. Macrophages and dendritic cells serve as antigen-presenting cells (APCs), activating T cells to prevent pathogen replication and spread. However, the immune system's potent clearance mechanisms can inadvertently reduce the deposition rate of inhaled drugs, potentially leading to excessive or adverse immune responses (Blank et al., 2017).

Designing drugs that mitigate adverse immune effects while harnessing immunomodulatory properties is crucial for the efficacy of inhalation therapy. Achieving this balance ensures that therapy remains effective without triggering counterproductive immune reactions.

By addressing these challenges, inhalation therapy can unlock its full potential, providing effective and targeted treatment for chronic respiratory diseases.

Novel Inhalation Formulations in Pulmonary Fibrosis

Inhalation therapy has demonstrated significant efficacy in treating various lung diseases. However, overcoming the challenges associated with this therapeutic approach necessitates ongoing research and innovative strategies. One primary objective is to reverse the pathological processes underlying numerous pulmonary disorders, particularly pulmonary fibrosis (PF). Novel inhalation therapies present a promising approach to achieve this goal. Thus, it is crucial to review current advancements in inhalation therapy for PF treatment and explore potential directions for future research.

Agonists or Inhibitors

The Nrf2 pathway and its downstream oxidative-antioxidant signaling pathways, along with the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) inflammatory signaling pathways, play pivotal roles in the progression and development of PF. Enhancing antioxidant defenses and inhibiting inflammatory pathways can mitigate PF. Consequently, activators of antioxidant factors and inhibitors of inflammatory proteins have been frequently utilized in research.

Nrf2 serves as a key regulator of cellular antioxidant responses and redox homeostasis. Utilizing Nrf2 activators can effectively suppress PF and significantly alleviate its symptoms in both in vitro and in vivo studies (Liu et al., 2021). Dimethyl fumarate (DMF), a first-generation Nrf2 activator, exemplifies this approach. Muralidharan et al. developed DMF

nanoparticles (NPs) and microparticles (MPs) through spray drying (SD) and co-SD techniques, analyzing their geometric size, morphology, moisture content, and microscopic spectra via scanning electron microscopy (SEM), X-ray powder diffraction, Karl Fischer titration (KFT), confocal Raman spectroscopy (CRM), and next-generation impactors. Their findings revealed that DMF NPs and MPs exhibited stable particle sizes and high airway deposition rates. Additionally, Liu et al. constructed a reactive oxygen species (ROS)-responsive nanoplatform (DSPE-PEG2000-ROS-sensitive linker thioketal [TK]) to deliver DMF. Using this platform, they treated bleomycin (BLM)-induced PF mice (administered every three days for 14 days starting on day 10). The results demonstrated that inhalation of the drug activated the Nrf2/HO-1 signaling pathway, balanced superoxide dismutase (SOD) and ROS levels, reduced the PF score, decreased M2 macrophage populations, and limited TGF-β secretion, ultimately improving the mice's condition. Similarly, the inhalation of a PI3K inhibitor (CL27c) was found to significantly enhance lung functions, including forced vital capacity (FVC), total lung capacity, and deep inhalation volumes, in BLM-induced PF mice (Campa et al., 2018).

BLM administration via the airway is a widely used model for studying PF. However, this model has inherent limitations and does not fully replicate the pathological processes observed in human idiopathic pulmonary fibrosis (IPF). In most animal species, a single BLM dose induces a rapid progression from pulmonary injury to fibrosis, with the latter peaking within weeks and subsequently resolving spontaneously. This differs significantly from the chronic, progressive nature of human IPF, which often develops over months or years and progresses to irreversible fibrosis. Furthermore, therapeutic interventions in animal models often target the pre-fibrotic phase, whereas human IPF patients are typically diagnosed after significant fibrosis has occurred. The model's inability to replicate the covert progression of human IPF limits its predictive validity. Additionally, the upregulation of specific transport proteins by BLM can induce drug efflux, thereby reducing experimental drug exposure and reliability of preclinical findings. Thus, developing animal models that closely mimic the chronic, progressive, and irreversible characteristics of human IPF is imperative for accurate drug evaluation and development.

In addition to targeting oxidative and inflammatory pathways, specific protein inhibitors offer critical intervention opportunities. Studies have revealed that αvβ6 integrin is significantly upregulated in IPF patients and facilitates disease progression by activating TGF-β. As a result, αvβ6 inhibitors are considered vital therapeutic targets for IPF. GSK3008348, a small-molecule αvβ6 inhibitor, has been shown to strongly suppress TGF-β secretion and slow PF progression. In vivo studies demonstrated the efficacy of GSK3008348 when administered via inhalation. These findings indicate that inflammatory and oxidative stress pathways are central to IPF pathogenesis, and that inhalation of targeted agonists or inhibitors may be a viable intervention strategy. Collectively, these results highlight the importance of modulating multiple signaling pathways to treat PF effectively.

Nanomedicine Platform

Nanomedicine involves the use of nanoscale particles, created through advanced nanofabrication techniques, as drug delivery systems or active pharmaceutical ingredients. This field encompasses direct application of nano-sized drugs and nanocarrier systems. The former includes the preparation of drug nanoparticles (NPs) via nanoscale precipitation or ultrafine grinding, while the latter involves combining drugs with carrier materials through processes like dissolution, dispersion, encapsulation, adsorption, or coupling to create nanodispersions. These nanodispersions primarily consist of polymers, lipid-based nanoparticles, dendritic macromolecules, microspheres and magnetic nanoparticles. The final product or carrier material in nanomedicine typically exhibits a nanoscale external size, internal structure, or surface structure (i.e., <100 nm), although particles with sizes below 1000 nm demonstrating

clear size-dependent effects are also included. Additionally, drug particles on the micrometer scale are discussed in this context.

Recent studies have explored the application of inhaled nanomedicine for pulmonary delivery using devices such as nebulizers, pressurized metered-dose inhalers (pMDIs), and dry powder inhalers (DPIs). Compared to conventional inhalation therapies, nanomedicine offers unique advantages. Firstly, MPs (1–500 nm) and NPs achieve higher lung deposition rates due to their reduced size. Secondly, NPs are better equipped to traverse biological barriers. Alveolar macrophages (AMs), key cells involved in particle clearance, demonstrate relatively limited phagocytosis of NPs, leading to prolonged lung retention and sustained drug release. In vivo studies have revealed that rat AMs engulf fewer particles <1 μm compared to those ranging from 1–5 μm. Thirdly, specific properties and surface modifications of NPs can further reduce their uptake by AMs. For instance, particles containing cholesterol and sphingolipids, NPs with neutral surface charges, soft and porous particles, hydrophilic particles, and NPs modified with polyethylene glycol (PEG) or dipalmitoyl phospholipids (DPPC) can evade AM clearance (Patel et al., 2015). Given these properties, MPs and NPs hold promise as effective therapeutic interventions for PF via inhalation delivery systems.

Drug Nano-Size Systems

The transformation of traditional Chinese medicine (TCM) monomers into microparticles (MPs) and nanoparticles (NPs) has been extensively studied in preclinical investigations for pulmonary fibrosis (PF) treatment. Various active ingredients in TCM, including curcumin, cryptotanshinone, and tetrandrine, have demonstrated anti-PF properties by targeting multiple pathways. Additionally, dry powder and nebulized formulations of TCM monomers, such as salvia polyphenolic acid and Panax ginseng total saponins, have been developed for PF intervention. Curcumin, a bioactive component derived from *Curcuma longa*, has been utilized in these approaches. Hu et al. developed a targeted drug delivery system for PF treatment using curcumin-loaded large porous MPs (curcumin-LPMPs), produced via the water-in-oil-in-water (W/O/W) emulsion method. These curcumin-LPMPs were further processed into dry powder capsules (30 mg/capsule) for inhalation via a dry powder inhaler. Both curcumin in dry powder form and curcumin-LPMPs showed antifibrotic effects, likely by inhibiting the NF-κB inflammatory pathway. However, curcumin-LPMPs demonstrated superior therapeutic outcomes due to higher lung deposition rates and reduced macrophage uptake, suggesting potential utility in targeted PF therapy. Hemmati et al. prepared dry curcumin-NPs (275 nm) by freeze-drying a mixture of β-cyclodextrin (40 mg) in deionized water and curcumin (12 mg) in acetone. Inhalation of curcumin-NPs (50 μg/kg, 100 μg/kg, and 200 μg/kg) over 21 consecutive days significantly alleviated bleomycin (BLM)-induced PF by reducing pulmonary inflammatory cell infiltration, hydroxyproline content, and cytokine levels, including tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), and platelet-derived growth factor (PDGF). Chen et al. formulated curcumin-loaded mesoporous polydopamine NPs (CMPN) through emulsion-induced interface polymerization. Polydopamine (PDA), a biocompatible polymer, was modified to produce mesoporous PDA (MPDA) with enhanced drug-loading capacity and efficient lung deposition post-inhalation. The CMPN, obtained via vacuum drying, demonstrated antioxidative and anti-inflammatory properties, thereby mitigating radiation-induced pneumonitis. As radiotherapy is a prevalent cancer treatment method, the associated lung injuries, such as pneumonitis and PF, often limit its applicability.

Although nano- and micro-sized drug formulations can enhance efficacy and reduce side effects, converting drugs into inhalable forms alone does not ensure optimal particle size and deposition rates. Optimization of excipients, ratios, and conversion techniques is essential for effective inhalable drug development. This is evident in the studies involving pirfenidone

(PFD) and swellable MPs (SMPs). Kang et al. converted PFD into inhalable dry particles using co-spray drying methods, including spray-dried (SD) PFD, and co-spray drying PFD with L-leucine (SD-PL), NaCl (SF-PN), or mannitol (SD-PM). Among these, SD-PL (1:1) yielded the smallest particle size (Dv50: 4.28 μm) and the highest aerosol performance (3.85 ± 0.21 μm). Adding 10% L-leucine (LL) as an excipient or incorporating SMPs optimized aerosol properties like flowability and expandability. In another study, a carrier solution composed of chitosan (CS) and LL in a 9:1 ratio was processed via high-pressure homogenization and spray drying to produce CS-SMPs. This formulation achieved improved anti-humidity properties, flowability, yield, and nebulization efficiency. The CS-SMPs (particle size: 464.4 ± 10.1 nm) demonstrated prolonged lung drug retention of up to 24 hours in PF rats, achieving therapeutic effects comparable to an oral dose at only 1/60 of the quantity. These effects were mediated via modulation of the TGF-β1/Smad3, STAT3, and sirtuin 3 (SIRT3) signaling pathways (Kang et al., 2022).

Drug Nano-Carrier Delivery Systems

Polymeric Nanoparticles: Polymeric nanoparticles (PNPs) are composed of synthetic or natural polymers and are widely utilized in inhalation therapies for PF. Polymers such as polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), polycaprolactone (PCL), albumin, gelatin, alginate, chitosan (CS), and agarose are commonly used for PNP synthesis. These PNPs enhance lung deposition and drug absorption by modulating hydrophobicity and surface charge properties based on the polymer type (Pinto Reis et al., 2006).

Nebulized PNPs: Nebulized PNPs have been extensively studied for inhalation delivery in PF treatment. Tacrolimus (Tac), an immunosuppressant, has shown efficacy in alleviating PF by reducing inflammation and improving pulmonary vascular permeability. Subsequent studies explored Tac-encapsulated NPs for inhalation therapy. Seo et al. utilized albumin NPs (Tac Alb-NPs) to encapsulate Tac and administered them via microspray aerosolizer to bleomycin-induced PF mice for 18 consecutive days. The Alb-NPs (182.1 ± 28.5 nm) achieved >80% drug encapsulation, with lung deposition lasting approximately 48 hours. Tac Alb-NPs significantly reduced pulmonary hydroxyproline (HYP) levels and inflammation, showing better outcomes than intraperitoneal administration. Similarly, Lee et al. demonstrated that Tac-loaded PLGA NPs modified with CS (CTS Tac PLGA-NPs) prolonged lung retention post-inhalation to 96 hours and provided better collagen reduction compared to oral administration.

The cationic nature of CS enhances bioadhesion and drug delivery performance, and its modification further improves nanoparticle viability and compatibility. Elkomy et al. optimized CTS-PLGA-NPs loaded with nifedipine (NFD) using a formulation containing 0.52% ω/υ PLGA, 1.5% ω/υ PVA, and 0.25% ω/υ CS. Continuous inhalation of NFD-CTS-PLGA-NPs for three weeks in PF rats resulted in efficient lung deposition (mass median aerodynamic diameter of 1.12 ± 0.28 μm and fine particle fraction of 80.48 ± 8.46%). This treatment reduced oxidative stress and fibrosis indicators by inhibiting the TGF-β/β-Catenin signaling pathway.

Polymer-based nanogels, such as those made from CS and alginate, offer stable drug encapsulation, high bioavailability, and good solubility. Chen et al. co-constructed quercetin (QU), a potent antioxidant and anti-inflammatory agent, with alginate nanogels using Ca2+ and hydrogen bonding. The resulting QU-alginate nanogels (<100 nm) were administered via ultrasonic aerosol inhalation for 3–7 days to treat paraquat-induced acute lung injury (ALI) in rats. These nebulized nanogels exhibited strong antioxidative and anti-inflammatory effects, reversing ALI and inhibiting PF progression.

Gene Therapy: Gene therapy holds promise for treating lung diseases such as idiopathic pulmonary fibrosis (IPF). Aerosolized gene therapy approaches, including CRISPR/Cas9, mRNA, siRNA, plasmid DNA (pDNA), and protein-based methods, are under investigation. For instance, PEG-PLGA-NPs carrying siRNA against IL-11 (siIL11) showed significant

antifibrotic effects in PF models by inhibiting myofibroblast biomarkers like collagen type I alpha 1 chain (COLIA1) and actin alpha 2, smooth muscle (ACTA2), while improving pulmonary function parameters such as respiratory resistance and elastance. Another study utilized mRNA encoding matrix metalloproteinase 13 (mMMP13)-keratinocyte growth factor (KGF) delivered using PEG-NPs (mMMP13-KGF-PEG-NPs) to PF mice. The treatment significantly improved PF by promoting alveolar re-epithelialization and enhancing aquaporin 5 (AQP5) to surfactant protein C (SP-C) ratios compared to nebulized and oral pirfenidone treatments. With continued research, inhalation-based gene therapy may emerge as a crucial tool for personalized IPF treatment.

Dry Powder Inhalation

Nanoparticles (NPs) are commonly utilized for chronic pulmonary fibrosis (CPF) intervention through dry powder inhalation, employing various drying techniques. Inhalation of antibiotics is a preferred strategy for CPF management as it ensures maximum airway deposition while minimizing the adverse effects of systemic drug exposure. However, the mucus barrier significantly impairs the efficacy of inhaled antibiotics. Consequently, numerous researchers have leveraged nanocarriers to deliver multiple antibiotics across the mucus layer to achieve effective anti-infective action. Ungaro et al. encapsulated tobramycin (Tb) in chitosan nanoparticles (CTS-NPs) and poly(vinyl alcohol)-alginate/poly(lactic-co-glycolic acid) nanoparticles (PLGA-NPs) and subsequently transformed them into dry powders using spray drying (SD). The Tb-poly(vinyl alcohol)-alginate/PLGA-NPs demonstrated enhanced deposition in the lower airways of the lungs in vivo, indicating that PLGA NP-based dry powder formulations are superior for inhaled antibiotics. Similarly, Juntke et al. used a biofilm model of human cystic fibrosis cells infected with *Pseudomonas aeruginosa* and observed that ciprofloxacin-PLGA-NPs eradicated planktonic bacteria and significantly reduced pathogen biofilm within one hour of intervention (Juntke et al., 2021).

Lipid-Based Nanocarriers

The lipid nanoparticle (LNP) system, described by Fonseca-Santos et al., primarily comprises solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). SLNs represent the first generation of lipid nanocarriers and are generally formulated using physiologically compatible lipids or lipid-like substances as pharmaceutical excipients. SLNs offer the advantages of various nanocarriers, including polymeric nanoparticles (PNPs), fat emulsions, and liposomes, making them well-suited for delivering lipophilic drugs. They exhibit high biocompatibility and effective slow-release properties. However, their limitations include low drug penetration ability, poor physical stability, and limited drug loading capacity (1–5%). These drawbacks suggest that while SLNs demonstrate therapeutic potential, they may not be suitable for all drug delivery applications.

NLCs, the second-generation lipid nanocarriers, address the limitations of SLNs by enhancing drug loading capacity and physical stability. NLCs are categorized into three types: imperfect, amorphous, and multiple types. Variations in lipid organization within the nanoparticles influence their physicochemical properties and drug-loading capabilities. Lipid-drug conjugates (LDCs) and polymer-lipid hybrid nanoparticles (PLNs) are integral to the NLC system. LDCs involve lipophilic modifications of water-soluble drugs or difficult-to-deliver compounds covalently attached to lipids, conferring drug-forming properties. The lipid materials used in conjugation include fatty acids, glycerides, and phospholipids. LDCs address the challenge of low encapsulation rates of water-soluble drugs in SLNs and NLCs. PLNs are optimized SLNs formed by introducing negatively charged polymers that create drug-polymer complexes encapsulated in hydrophobic lipid materials. Hybridization of polymers and lipids

typically involves hydrophobic interactions, van der Waals forces, electrostatic interactions, and covalent bonding, combining the benefits of liposomes and nanoparticles.

Notably, numerous studies on lipid-based nanocarriers for inhalation treatment of idiopathic pulmonary fibrosis (IPF) have demonstrated promising outcomes. Prostaglandin E2 (PGE2), recognized for its pro-inflammatory and tissue repair effects in the lungs, has been evaluated as a potential drug for IPF treatment. However, systemic delivery is limited by its short half-life in the blood and poor lung distribution. In 2017, Garbuzenko et al. formulated nebulized PGE2-siRNA-NLCs containing PGE2 and three siRNAs targeting MMP3, CCL12, and HIF1A for treating bleomycin (BLM)-induced pulmonary fibrosis (PF) in mice. Administered twice weekly for three weeks, this combination yielded significant anti-fibrotic effects, demonstrating the successful integration of nanoparticle delivery and gene therapy (Garbuzenko et al., 2017). INS1009, a vasodilator releasing hexadecyl-treprostinil (C16TR) from LNPs, also displayed potential. C16TR, activated by endogenous lung esterase, is converted to treprostinil (TRE), a PGE2 agonist with anti-fibrotic properties. Corboz et al. showed significant dose-dependent reductions in collagen deposition in BLM-induced IPF mice following inhalation of INS1009.

Lipid nanoparticles have also addressed multi-drug resistance in bacterial infections, particularly in CPF patients. *P. aeruginosa*'s resistance mechanisms exacerbate the challenge of antibiotic therapy in CPF. Garbuzenko et al. developed PEGylated NLCs loaded with lumacaftor and ivacaftor for CPF treatment. Nebulized via a one-jet collision nebulizer, these formulations markedly reduced or resolved lung lesions in CPF mice. However, effective drug delivery through thick sputum to the lesion remains challenging in clinical practice. *P. aeruginosa* produces virulence factors via quorum sensing (QS), and QS inhibitors (QSIs) effectively mitigate its virulence. Nafee et al. demonstrated that QSI-loaded SLNs could penetrate mucus, exhibited high stability and anti-toxicity, and were safe for use. These nanoparticles (<100 nm), nebulized by an ultrasonic nebulizer, showed superior efficacy compared to blank SLNs. NLCs loaded with tobramycin (Tb-NLCs) demonstrated an encapsulation rate of up to 93%, achieving uniform, long-lasting distribution in mouse lungs post-nebulization. Zhang et al. addressed nanoparticle stability issues post-nebulization by evaluating various mRNA-LNP formulations. Their findings revealed that mRNA-LNPs delivered via nebulization maintained stability in particle size, zeta potential, drug encapsulation rate, and intracellular protein expression, offering valuable insights into developing effective strategies for PF treatment.

Other Novel Inhalation Drugs

In addition to the aforementioned therapies, new inhalation interventions show promise for PF treatment. Inhaled gases, such as hydrogen (H2) and nitric oxide (NO), exhibit therapeutic potential. H2's antioxidant and anti-inflammatory effects alleviate conditions such as ischemic brain injury, myocardial ischemia-reperfusion injury, and sepsis-induced liver injury. In PF models, H2 inhalation reduced pro-fibrotic factors like TGF-β1 and TNF-α, inhibited epithelial-to-mesenchymal transition (EMT), and improved macrophage polarization and lung functions. Slow-releasing NO donors, such as diethylenetriamine nitric oxide adduct (DETA/NO), significantly reduced myofibroblasts and type I collagen deposition in PF mice following 13 days of inhalation therapy.

Extracellular vesicles (EVs), small structures capable of transporting proteins and nucleic acids, regulate intercellular communication and influence cellular behavior. Exosomes from mesenchymal stem cells and macrophages have been studied for PF treatment, primarily using intravenous injections or airway instillation. Dinh et al. introduced exosome inhalation therapy in PF mice using a compressed nebulizer. Inhaled exosomes improved lung function, reduced inflammatory markers, and alleviated PF in these models.

Conclusion

Pulmonary fibrosis (PF) remains a challenging condition, characterized by progressive scarring of lung tissue and limited therapeutic options. Advances in respiratory therapy, particularly inhalation-based strategies, have shown significant potential in addressing this debilitating disease. Innovations such as nanoparticle-based drug delivery, dry powder inhalers, lipid-based nanocarriers, and gene therapies are transforming how drugs are administered, improving lung deposition, bioavailability, and therapeutic outcomes. These approaches mitigate systemic side effects while enabling targeted treatment of fibrotic lesions.

Despite these promising advancements, challenges persist, including optimizing drug stability, overcoming biological barriers, and ensuring efficient delivery through mucus layers. The integration of inhalation therapies with nanotechnology, extracellular vesicles, and innovative gases like hydrogen and nitric oxide exemplifies the multifaceted efforts to enhance treatment efficacy.

Ongoing research and clinical trials continue to refine these methods, paving the way for personalized and precision respiratory therapies. With sustained investment and interdisciplinary collaboration, inhalation therapy stands poised to redefine the landscape of pulmonary fibrosis management, offering hope for improved patient outcomes and quality of life.

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