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Progress in Utilizing Chitosan-Based Nanoparticles for Pulmonary Drug Administration

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Abstract

The escalating prevalence of respiratory ailments poses a significant global public health challenge, ranking among the primary causes of mortality worldwide. Notably, diseases such as asthma, chronic obstructive pulmonary disease, pneumonia, cystic fibrosis, and lung cancer, alongside the emergence of respiratory diseases, notably those induced by the coronavirus family, have contributed substantially to global fatalities in the past two decades. Consequently, numerous studies have been undertaken to enhance the effectiveness of therapeutic interventions against these diseases, with a particular emphasis on nanomedicine-driven pulmonary drug delivery. As a result, the development of nanocarriers has emerged as a promising avenue to surmount the constraints associated with traditional therapies, aiming to elevate drug bioavailability at the intended site while minimizing undesired side effects. Within this domain, nanoparticles fashioned from chitosan (CS) exhibit distinct advantages over alternative nanocarriers owing to the inherent biological properties of chitosan, including its anti-inflammatory, antimicrobial, and mucoadhesive attributes. Furthermore, CS nanoparticles have demonstrated the potential to augment drug stability, extend the duration of action, refine drug targeting, regulate drug release kinetics, optimize the dissolution of poorly soluble drugs, and enhance the cell membrane permeability of hydrophobic drugs. These unique properties position CS nanoparticles as a promising candidate for optimizing drug performance following pulmonary administration. Consequently, this review endeavors to elucidate the potential of chitosan nanoparticles in the realm of pulmonary drug delivery, shedding light on how their intrinsic biological characteristics can ameliorate the treatment landscape of pulmonary diseases. Emphasis is placed on delineating the synergistic interplay between chitosan nanoparticles and the encapsulated drug, thereby offering insights into the prospective advancements in treating respiratory ailments.

Key Words: Lung diseases, Pulmonary, Drug delivery, Chitosan, Nanoparticles

Akciğer Hastalıklarında Kitosan Tabanlı Nanopartiküllerin İlaç Taşıyıcı Sistemlerin Uygulamasındaki Gelişmeler

Özet

Solunum yolu hastalıklarının giderek artan yaygınlığı, dünya genelinde önemli bir küresel halk sağlığı sorunu teşkil ederek dünya genelindeki başlıca ölüm nedenleri arasında yer almaktadır. Özellikle son iki on yılda astım, kronik obstrüktif akciğer hastalığı, pnömoni, kistik fibrozis ve akciğer kanseri gibi hastalıkların yanı sıra koronavirüs ailesi tarafından tetiklenen solunum yolu hastalıkları gibi hastalıklar, küresel ölümlere büyük ölçüde katkıda bulunmuştur. Bu nedenle, bu hastalıklara yönelik terapötik müdahalelerin etkinliğini artırmaya yönelik birçok çalışma yapılmış, bu çalışmaların özellikle nanotıp destekli akciğer ilaç dağıtımına odaklandığı gözlemlenmiştir. Bu bağlamda, nanonakliyecilerin geliştirilmesi, geleneksel tedavilerle ilişkilendirilen kısıtlamaları aşmak için umut vaat eden bir yol olarak ortaya çıkmış ve böylece amaçlanan bölgede ilaç biyoyararlılığını artırmayı ve istenmeyen yan etkileri en aza indirmeyi hedeflemiştir. Kitosan (CS) kullanılarak şekillendirilen nanopartiküller, kitosanın doğal biyolojik özelliklerine dayalı olarak diğer nanonakliyecilere göre önemli avantajlar sunmaktadır. Bu avantajlar arasında anti-enflamatuar, antimikrobiyal ve mukoadhezif özellikler yer almaktadır. Ayrıca, CS nanopartiküller, ilaç kararlılığını artırma, etki süresini uzatma, ilaç hedeflemeyi iyileştirme, ilaç salınım kinetiğini düzenleme, düşük çözünürlüğe sahip ilaçların çözünürlüğünü artırma ve hidrofobik ilaçların hücre zarı geçirgenliğini artırma potansiyeline sahiptir. Bu benzersiz özellikler, CS nanopartiküllerini akciğer uygulaması sonrası ilaç performansını optimize etmek için umut vadeden bir aday olarak konumlandırmaktadır. Bu nedenle, bu inceleme, kitosan nanopartiküllerinin akciğer ilaç dağıtımı alanındaki potansiyelini aydınlatmayı amaçlamakta ve kitosanın içsel biyolojik özelliklerinin solunum yolu hastalıklarının tedavi alanını nasıl iyileştirebileceğine dair anlayış sunmaktadır. Ayrıca, CS nanopartiküllerinin içinde bulunduğu ilaç ile olan etkileşimi ayrıntılı olarak ele alarak solunum yolu hastalıklarının tedavisindeki olası ilerlemelere dair bir perspektif sunulmaktadır.

Anahtar Kelimeler: Akciğer hastalıkları, Akciğer, İlaç dağıtımı, Kitosan, Nanopartiküller

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INTRODUCTION

Lung diseases rank among the top 10 global causes of mortality, with Chronic Obstructive Pulmonary Disease (COPD), lower respiratory tract infections, and lung cancer standing as the third, fourth, and sixth leading causes of death, respectively (1). The advent of the COVID-19 pandemic has further exacerbated respiratory-related fatalities, with the surge in severe respiratory symptoms and associated complications among individuals infected with SARS-CoV-2 (1,2). Additionally pandemic control measures, such as social distancing and lockdowns, may have contributed to delays in diagnosing and treating non-coronavirus-related lung diseases, elevating the risks of complications and mortality associated with these conditions (3).

Consequently, there has been a heightened focus on the research and development of Pulmonary Drug Delivery Systems (PDDS) in recent years to optimize the treatment of lung diseases. PDDS offers several advantages, including targeted local treatment, maintaining high drug concentrations in the lungs for enhanced therapeutic efficacy, controlled drug release, and improved patient compliance (4). However, delivering drugs to the lungs presents significant challenges, necessitating the overcoming of mechanical, chemical, and immunological barriers of the respiratory tract (5,6). Various strategies, including nanostructured carriers, have been developed to address these challenges, capitalizing on their reduced size and increased surface-to-volume ratio to facilitate effective drug absorption and mitigate lung clearance (7,8,9).

Among nanostructures, polymeric nanoparticles, particularly those made from chitosan (CS), have gained widespread attention due to their biocompatibility, biodegradability, low toxicity, and scalability (10,11,12,13). CS, a natural polymer, stands out for drug delivery applications, especially in pulmonary delivery, owing to its inherent properties, such as mucoadhesive potential, and antimicrobial, anti-inflammatory, antioxidant, and wound-healing activities (14,15). Furthermore, the FDA has recognized CS as

"GenerallyRecognized as Safe" (GRAS), approving its use in tissue engineering and drug delivery devices (16).

CS nanoparticles exhibit the capacity to enhance drug stability, prolong action duration, control drug release, optimize dissolution of poorly soluble drugs, and increase cell membrane permeability for hydrophobic drugs. Additionally functionalization of CS nanoparticles can enhance adhesion to lung cells, enabling targeted drug delivery and minimizing systemic side effects (17). This advancement in drug delivery technology holds significant promise for treating chronic lung diseases like asthma and COPD, as well as improving drug delivery for bacterial and fungal infections and lung cancer.

Several studies support the potential of CS nanoparticles in diverse applications, including improving drug transport in a murine asthma model (18), enhancing in vivo lung deposition for COPD treatment (19), inhibiting *P. aeruginosa* biofilm (20), reducing inflammatory responses in cystic fibrosis (CF) (21), improving drug selectivity in lung cancer cells (22), increasing antituberculostatic drug concentration in the lung (15), and reducing systemic toxicity in severe COVID-19 infections (23,24,25).

This comprehensive review delves into the advantages and prospects of CS nanoparticles as pulmonary drug delivery systems, encompassing small molecule drugs, proteins/peptides, and genes for treating local lung diseases. The data collection spanned the years 2013 to 2023 and involved sources such as Scopus, Web of Science, Science Direct, PubMed, and Espacenet.

Challenges and Opportunities in Pulmonary Drug Delivery

The pulmonary route stands out as a promising avenue for drug administration, offering advantages over conventional dosage forms by allowing a reduction in the administered dose compared to oral and parenteral routes. Key characteristics of the pulmonary route, such as a substantial surface area (100 m^2), abundant blood supply, high permeability of the thin peripheral epithelial layer (0.2–0.7 μm), low enzymatic activity, and the avoidance of first-pass metabolism, contribute to its efficacy (26). Despite these advantages, challenges exist in harnessing the full therapeutic potential of pulmonary drug delivery, both for local and systemic treatments.

A significant obstacle in pulmonary drug delivery is the intricate clearance mechanisms that drugs encounter upon inhalation, acting as primary barriers to drug absorption. Mucociliary clearance, a crucial defense mechanism of the lung, entraps inhaled molecules in the mucus layer, impacting their solubility, diffusion across epithelial layers, and binding to cell surfaces or

receptors. Drugs unable to penetrate the mucus layer face removal through mucociliary clearance, emphasizing the importance of crossing this barrier to reach the alveolar epithelial layer (27). Particle properties, including size and surface area, play a vital role in determining the efficiency of drug delivery systems, prompting investigations into the use of (CS) nanoparticles. CS, known for its mucoadhesive properties, facilitates drug penetration through the mucus layer by interacting with mucin (28-29).

Pulmonary surfactant, a lipoprotein complex produced by alveolar cells, can enhance drug adhesion and agglutination, potentially increasing drug clearance from the lungs (30). Recent studies, however, suggest that pulmonary surfactant is not an insurmountable barrier and can serve as an effective vehicle for delivering both hydrophobic and hydrophilic compounds deep into the lungs (31,32).

Pulmonary macrophages present another challenge to drug efficacy in the lungs, particularly for particles in the size range of 0.5 to 5.0 μm, which are prone to internalization through endocytosis. Despite this challenge, recent research has identified pulmonary macrophages as a therapeutic target, particularly in the treatment of tuberculosis. For instance, Pawde and colleagues46 developed mannose-functionalized CS nanoparticles containing clofazimine for treating drug-resistant tuberculosis. The mannose-decorated nanoparticles facilitated increased recognition by macrophages, enhancing uptake and enabling targeted drug delivery to the site of Mycobacterium tuberculosis infection. This underscores the potential for overcoming challenges and leveraging opportunities in pulmonary drug delivery systems.

Physicochemical and Biological Properties of Chitosan

CS is a linear amino polysaccharide characterized by the repetition of 2-amino-2-deoxy-β-(1,4)-d-glucosamine and 2-acetamide-2-deoxy-β-(1,4)-d-glucosamine units, resulting from the partial deacetylation of chitin under alkaline conditions. Chitin, the precursor of CS, is composed of the polymer poly (β-(1,4)-N-acetyl-D-glucosamine) and is abundantly present in the exoskeleton of crustaceans, insects, arthropods, and the cell walls of fungi. Notably, marine chitin derived from sources such as shrimp, lobster, and crab stands as the primary commercially available source of CS (33,34).

CS stands as a linear polycationic polymer with free acetamide groups and hydroxyl functions attached to the glucopyranose rings. This structure, formed by the partial deacetylation of chitin, exhibits susceptibility to nucleophilic attacks. Selective modification of the free amino groups in CS results in a diverse range of

functionalities, distinguishing it from chitin. CS, derived primarily from marine chitin found in crustaceans, insects, arthropods, and fungi, offers superior hydrophilicity and reactivity compared to chitin. Additionally while chitin faces limitations due to its low aqueous solubility and reactivity, CS demonstrates enhanced hydrophilicity, excellent degradability, and biocompatibility (14,35).

CS is soluble in dilute acidic solutions, with solubility influenced by factors such as degree of deacetylation (DDA) and molecular weight (MW). However, exceeding the polymer's pKa results in deprotonation, causing CS to lose its positive charge and precipitate. The choice of acid for solubilization is critical, affecting physicochemical parameters like solubility, viscosity, ionic strength, and stability. Acetic acid is commonly used for adequate solubility, while citric acid and formic acid are alternative options. Acid selection can impact solution viscosity, ionic strength, and stability, affecting interactions with other compounds. Furthermore, acid type can influence CS nanoparticle formation through electrostatic interactions (36-41).

The crystallinity of CS, characterized by the crystallinity index (CI), involves the ratio of crystalline to amorphous fractions. CS exhibits semi-crystalline and polymorphic behavior, with CI influencing properties like swelling, porosity, hydration, and absorption. Molecular weight categorizes CS as low, medium, or high, impacting viscosity and solubility. Commercially available CS typically falls within the 50 to 2000 kDa range. The degree of deacetylation (DDA) plays a crucial role in determining CS's physicochemical properties, affecting solubility, viscosity, mechanical behavior, biodegradation, mucoadhesion, and antimicrobial activity. Reports indicate that mucoadhesive and antibacterial properties increase with higher DDA (42,43).

CS possesses various biological activities, including antimicrobial, antioxidant, anti-inflammatory, and anticancer properties. The antimicrobial mechanism involves interactions between positively charged CS molecules and negatively charged bacterial cell membranes, disrupting biofilms and causing cellular component leakage. Antioxidant activity involves the removal of free radicals, with CS exhibiting greater properties at lower molecular weights and higher DDA. Immunostimulatory effects result from the presence of N-acetyl-D-glucosamine groups, stimulating inflammatory cells and promoting cytokine production. CS also demonstrates anticancer activity by inhibiting proliferation, inducing apoptosis, and activating the immune system. CS's flexible structure, attributed to free protonable amino groups, enables easy modification and functionalization, making it a versatile polymer for nanoparticle development (17,44).

Preparation of Chitosan-Based Nanoparticles

Numerous methods have been devised for the synthesis of CS nanoparticles, with key approaches involving emulsification, precipitation, and ionic or covalent crosslinking, often implemented in combination (45). The initial method, utilizing covalent crosslinking with glutaraldehyde, was later discarded due to toxicity concerns and drug integrity issues (46-47).

Precipitation Methods

Phase Inversion Precipitation: Involves emulsification using an aqueous CS solution, stabilizer (poloxamer), and organic phase, followed by high-pressure homogenization and low-pressure evaporation for nanoparticle precipitation (48).

Desolvation: Entails coalescence of water-in-oil emulsions, promoting nanoparticle precipitation. Organic solvents and high-energy homogenization limit widespread use, and resultant nanoparticles are typically larger (31,44).

Widely adopted for its simplicity, cost-effectiveness, environmental friendliness, and scalability. Electrostatic interactions between CS's positively charged amino groups and negatively charged polyanions, like sodium tripolyphosphate (TPP), form nanospheres. Particle size can be adjusted by varying the CS/TPP ratio. Although advantageous, it may yield larger nanoparticles with high polydispersity, and pH changes can destabilize the system (45).

Based on covalent crosslinking, this method utilizes reverse micelles as nanoreactors. Crosslinkers, such as glutaraldehyde, connect CS chains to form interconnected polymer aggregates. The technique offers controlled particle size distribution, producing smaller nanoparticles (<100 nm) compared to ionic gelation. However, glutaraldehyde's cytotoxicity prompts the exploration of alternative crosslinking agents like genipin (46-48).

Considered environmentally friendly, it involves dissolving CS in aqueous acetic acid and passing the solution through a nozzle with hot air. Parameters like nozzle size, flow rate, and temperature influence nanoparticle properties. Drawbacks include longer processing time, larger particle size, and suitability issues for thermosensitive drugs (49-50).

CS can serve as a coating for various nanostructures such as liposomes, solid lipid nanoparticles, and polymeric nanoparticles. Integration can occur during or after nanoparticle preparation, with CS solution dripped onto nanoparticle suspensions. Coating mechanisms involve entanglement of polymer chains or electrostatic interaction between CS and nanoparticle surfaces (41-45).

Chitosan-Based Nanoparticles for Pulmonary Delivery

The utilization of CS nanoparticles for pulmonary delivery encounters challenges, primarily stemming from their proclivity to aggregate and undergo exhalation. To surmount these challenges and establish a stable, solid formulation, particle engineering techniques like freeze-drying and spray-drying have emerged as promising strategies. Incorporating carriers such as lactose and mannitol becomes crucial to producing dry inhalable powders, ensuring an optimal mean aerodynamic diameter for effective deposition in the alveoli, and preventing nanoparticle aggregation (48).

Given CS's intrinsic properties, including mucoadhesion, anti-inflammatory, and antimicrobial activities, CS nanoparticles offer significant advantages for local drug delivery to the lungs. These nanoparticles not only augment the antiviral (e.g., anti-SARS-CoV-2) and antibacterial (e.g., against M. tuberculosis) activities of encapsulated drugs but also facilitate drug penetration through the mucosal layer. Moreover, they enhance the anti-inflammatory effects of the drug and promote increased interaction/internalization in specific cells, such as macrophages and tumor cells.

Due to its unique properties and numerous advantages, several studies have been conducted to investigate the pulmonary delivery of drugs encapsulated in CS-based nanoparticles. A summary of key findings is presented in Table 1-2 (37-48).

Table 1. CS-based nanoparticles for pulmonary drug delivery

Disease	Drug	Limitations	Carrier	Main Results
Asthma	Ferulic Acid	Low bioavailability and short half-life	Hyaluronic acid-coated CS NP	Improved drug interaction and transport across the mucus layer; increased therapeutic efficacy
	Budesonide	Low bioavailability	CS-coated PLGA NP	Improved bioavailability and in vivo lung deposition in animal model
	Baicalein	Low bioavailability	CS NP	Nanoparticles control the immune-allergy-inflammatory response of asthma in mice
	Montelukast	Significant hepatic metabolism after oral administration	CS NP	DPI formulation showed Optimum deposition in the deep lung
COPD	Budesonide	Low aqueous solubility and bioavailability	CS NP	Enhancement of drug solubility
	Amikacin	Poor lung penetration after endovenous administration	PEG-CS NP combined with black phosphorus quantum dots	Improved mucus penetration and antibacterial activity
Pulmonary fibrosis	Nifedipine	Low bioavailability	CS-PLGA NP	Reduced markers of pulmonary fibrosis and oxidative stress
IPF	msFGFR2c	Low bioavailability	Phosphoryl-choline-CS NP	Enhanced antifibrotic efficacy, reduced inflammatory cytokines, decreased pulmonary fibrosis score and collagen deposition

Table 2. (Table 1, continuation)

Disease	Drug	Limitations	Carrier	Main Results
CF	Ciprofloxacin	Microbial resistance	ALG-lyase-functionalized CS NP	Higher inhibitory effect on P. aeruginosa biofilm
	wtCFTR-mRNA	Low stability; low transfection efficiency	CS-lecithin oil-core nanocapsules	Restored CFTR function in the cystic fibrosis cell line
	Antisense oligonucleotide (ASO)	Low stability	CS/ASO nanocomplex	Significant downregulation of ENaC activity in human respiratory epithelial cells
	Tobramycin	High frequency of administration; ototoxic and nephrotoxic effects; bacterial resistance	SLPICS-functionalized ALG/CS NP	Inhibition of P. aeruginosa in vitro; reduction in inflammatory response; improvement in interaction with CF mucus
Pulmonary fibrosis	Nifedipine	Low bioavailability	CS-PLGA NP	Reduced markers of pulmonary fibrosis and oxidative stress
PF	msFGFR2c	Low bioavailability	Phosphoryl-choline-CS NP	Enhanced antifibrotic efficacy, reduced inflammatory cytokines, decreased pulmonary fibrosis score and collagen deposition
CF	Ciprofloxacin	Microbial resistance	ALG-lyase-functionalized CS NP	Higher inhibitory effect on P. aeruginosa biofilm
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	Antisense oligonucleotide (ASO)	Low stability	CS/ASO nanocomplex	Significant downregulation of ENaC activity in human respiratory epithelial cells
	Tobramycin	High frequency of administration; ototoxic and nephrotoxic effects; bacterial resistance	SLPICS-functionalized ALG/CS NP	Inhibition of P. aeruginosa in vitro; reduction in inflammatory response; improvement in interaction with CF mucus
	Ciprofloxacin	Microbial resistance	DNase-I-functionalized CS NP	Prolonged microbial inhibition, prevention of biofilm formation and biofilm dispersal potential
Lung cancer	Resveratrol	Low solubility	CS/lecithin nanocomplex	Enhanced antitumor activity; increased selectivity in A549 cells
	aPD-L1	Low stability; unwanted adverse effects	CS/aPD-L1 nanocomplex	Improved lung adhesion and permeation; enhanced therapeutic efficacy
Tuberculosis	Bedaquiline	Prolonged treatment; unwanted adverse effects	CS NP	Reduction in toxic effects; Increased drug concentration in the lungs
	Linezolid	Unwanted adverse effects	CS NPs	Improved deep lung deposition in vitro
Pneumonia	Gallium.Ga(III)	Nephrotoxicity	Hyaluronic acid-CS NP	Improvement in Ga(III) persistence in the lungs and preventing its accumulation in the kidney
	Gentamicin	Low bioavailability; unwanted adverse effects	CS/Fucoidan NP	Improved antibacterial activity; reduced systemic toxicity
RSV	Oxymatrine	Enzymatic degradation; poor lung penetration	CS-coated liposomes	Enhanced distribution and retention of oxymatrine in lung tissue in vivo
COVID-19	Silymarin and curcumin	Low penetration and adsorption in the lungs	CS-coated BSA NP	Reduced inflammation; enhanced antiviral activity in vitro

Asthma

Asthma is a complex respiratory disease characterized by irreversible airway obstruction, hyperresponsiveness, and chronic inflammation. Conventional treatments involve bronchodilators and glucocorticosteroids, but high doses can be clinically ineffective and harmful (18). Dhayanandamoorthy et al. developed CS nanoparticles loaded with ferulic acid (FA) and functionalized with hyaluronic acid (HA) for asthma prophylaxis. These nanoparticles, called FACHA, were aerosolized using a vibrating mesh nebulizer. In mouse models of ovalbumin-induced asthma, FACHA nanoparticles attenuated inflammation, hypersensitivity, and airway remodeling. Compared to free FA, FACHA nanoparticles exhibited superior therapeutic indices, attributed to HA-functionalized CS promoting better deposition and an improved therapeutic index of HA (19).

Budesonide (BUD), a poorly bioavailable drug used in asthma treatment, was loaded into CS-poly(lactic-co-glycolic acid) (PLGA) nanoparticles by Ahmad et al. The BUD-loaded nanoparticles (BUD-NP) demonstrated lung deposition and penetration. Inhalation of BUD-NP resulted in higher Cmax and AUC compared to oral and intravenous treatment groups. The improvement in BUD absorption was linked to the induction of intercellular tight junction openings within the lung epithelium facilitated by CS (20).

CS nanoparticles were also employed for the pulmonary delivery of baicalein, a flavonoid with anti-inflammatory properties. Baicalein-CS nanoparticles controlled eosinophilic inflammation, airway hyperresponsiveness, and immune-allergic responses in mouse models of asthma. The nanoparticles downregulated IL-5 levels, contributing to better-managed inflammation (49).

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a progressive inflammatory lung disease resulting in decreased lung function. Anti-inflammatory therapies, including corticosteroids like BUD, are commonly used. BUD-loaded CS nanoparticles (CS NP) were developed using ionic gelation with poly(vinyl alcohol) (PVA) as a surfactant. The spherical nanoparticles exhibited improved drug release in vitro, demonstrating potential for enhanced therapeutic outcomes in COPD.121 Black phosphorus quantum dots (BPQDs) associated with PEGylated CS nanospheres were used to deliver amikacin (AM) for treating pulmonary infections in COPD patients. The nanostructure exhibited mucoadhesive properties, facilitating mucus penetration and resulting in higher drug release due to the rapid degradation of BPQDs. This approach alleviated airflow obstruction in a COPD mice model (40-42).

Pulmonary Fibrosis

Pulmonary fibrosis involves the remodeling and destruction of lung tissue. Nifedipine, a calcium channel blocker, loaded into CS-PLGA nanoparticles, demonstrated promise for treating pulmonary fibrosis. The nanoparticles exhibited a spherical shape, improved drug release, enhanced lung deposition, and increased bioavailability. Engineered nanoparticles reduced lung fibrotic and oxidative stress markers, demonstrating potential therapeutic benefits (23). Phosphorylcholine-coated CS nanoparticles (PPCs-NPs) were developed to encapsulate the mutant soluble ectodomain of fibroblast growth factor receptor-2 IIIc (msFGFR2c) protein, targeting excessive myofibroblast differentiation in idiopathic pulmonary fibrosis (IPF). The nanoparticles significantly reduced α-smooth muscle actin (α-SMA) expression, a marker of myofibroblast differentiation. In vivo studies showed increased msFGFR2c bioavailability, improved therapeutic efficacy, and enhanced rat survival rates (24). These studies highlight the potential of CS nanoparticles in addressing various respiratory conditions, providing targeted and controlled drug delivery for improved therapeutic outcomes.

Cystic Fibrosis (CF)

CF is characterized by impaired mucociliary clearance due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leading to mucus retention, bacterial infection, inflammation, and airway obstruction. Patel et al. investigated ciprofloxacin-loaded alginate lyase functionalized-CS nanoparticles against mucoid P. aeruginosa biofilm. The alginate lyase disrupted bacterial mucus, enhancing ciprofloxacin delivery. The nanoparticles had suitable properties for pulmonary drug delivery, demonstrating antimicrobial and anti-biofilm potential (20).

Lung Cancer

Chemotherapy remains the primary treatment for advanced lung cancer, but traditional drugs face limitations like lack of targetability, low bioavailability, and severe side effects (21). CS nanoparticles are explored for cancer therapy due to their mucoadhesiveness, controlled release, targeting, and increased permeability into tumor cells. Kamel et al. developed CS-doped self-assembled lecithin-based cationic nanoparticles (LeciPlex) loaded with resveratrol, aiming to improve solubility and anticancer efficacy (22). The study reported enhanced anticancer effects, low toxicity, and increased selectivity against the A549 lung cancer cell line (23).

In another study, CS nanoparticles loaded with anti-programmed cell death protein ligand 1 (aPD-L1) were prepared for inhalation to treat lung cancer. CS facilitated transmucosal delivery, promoting the rapid accumulation of

aPD-L1 in lung metastasis. CS acted as an adjuvant for aPD-L1, inducing potent cell-mediated immune responses and reducing the number of metastases in the lungs (48).

These studies showcase the potential of CS nanoparticles in addressing challenges associated with CF and lung cancer, providing targeted and effective drug delivery strategies.

CONCLUSION

Due to the rising mortality associated with respiratory diseases like COVID-19, tuberculosis, and lung cancer, there has been a growing emphasis on developing innovative systems for delivering drugs to the lungs. In this context, nanostructured carriers, particularly CS nanoparticles, have gained attention as a promising alternative. The progress in pulmonary drug delivery using CS has been noteworthy, demonstrating significant achievements.

CS, widely acknowledged as a renewable resource, second only to cellulose, possesses distinctive properties, including being non-toxic, biocompatible, and biodegradable. These attributes provide a competitive edge over other biodegradable polymers, with mucoadhesive, anti-inflammatory, and antimicrobial activities. The antimicrobial properties of CS can be harnessed to combat resistance, such as in P. aeruginosa infections, while its anti-inflammatory nature may aid in reducing inflammation in severe acute respiratory syndrome. This review critically examines the advancements of CS-based nanoparticles as an inhaled drug delivery system.

These nanoparticles exhibit considerable potential for clinical use, offering benefits like improved local drug delivery, minimized side effects, enhanced therapeutic activity, and prolonged drug release. The promising results evaluated in this review highlight the ability of CS nanoparticles, when administered via inhalation, to address the significant challenge of drug clearance from the lungs. Several in vivo studies have reported an increase in drug deposition in the lungs, attributed to the crucial mucoadhesive property of CS, facilitating drug penetration through the mucus layer. Furthermore, CS nanoparticles optimize biopharmaceutical parameters, particularly solubility, contributing to increased bioavailability, with some studies reporting a reduction in systemic toxicity.

Moreover, CS nanoparticles enhance the therapeutic activity of drugs, particularly in terms of antibacterial activity against CF-related pathogens, antiviral activity against SARS-CoV-2, and anti-inflammatory activity needed for treating conditions like COPD, IPF, and CF. Collectively, these observed benefits position CS as a polymer with the most promising properties for the development of

nanocarriers for pulmonary drug delivery applications.

Nevertheless, further studies are imperative to establish scalable processes for CS nanoparticle preparation. Additionally surface engineering of CS nanoparticles using specific ligands should be explored to actively target these particles to specific lung sites. Comprehensive investigations into the pharmacokinetics, preclinical toxicity, and biodistribution parameters of CS nanoparticles are essential steps to move closer to conducting clinical trials.

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Concept: Design: Literature search: Data Collection and Processing: Analysis or Interpretation: Written by: GM, ZVS.

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