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Formulating for the lungs: recent trends in liquid, dry, and hybrid inhalation technologies

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Abstract. Pulmonary drug delivery has entered a new stage as nanoscale formulations are increasingly paired with modern inhalation devices to improve targeting within the lungs. This review focuses on how current technologies—such as liposomes, lipid nanoparticles, porous aerogel microparticles, and dry-powder systems—are being engineered to protect therapeutic cargo and navigate the physical barriers of the respiratory tract. We discuss key formulation choices, including controlling particle size in the 1–5 μm range, stabilizing nanoparticles during aerosolization, and designing surfaces that move more easily through mucus. Evidence from recent studies is also examined, from the clinical performance of inhaled liposomal antibiotics like Arikayce to experimental nucleic acid–based therapies that show promise in preclinical lung disease models. Together, these developments illustrate how device design and formulation strategy contribute to improved deposition, stability, and local drug activity in the lungs. The growing convergence of these approaches is shaping a more adaptable framework for future inhaled therapies and suggests that nanoscale systems will play an increasingly central role in treating respiratory disorders.

Keywords: Lipid Nanoparticles (LNPs), Dry Powder Inhalers (DPIs), biological aerogels, pulmonary drug delivery, controlled release, respiratory disease therapy

1. Introduction

Inhalation formulations play an indispensable role in pulmonary drug delivery, playing a pivotal part in dictating the success of therapeutic interventions. Their influence on aerosol generation, drug stability, deposition patterns, and absorption in the lungs significantly affects the efficacy and safety of respiratory medications. Enhancing the solubility and bioavailability of drugs with low solubility is a critical challenge in inhalation therapy, and one effective strategy to address this is by incorporating lipid-based nanocarriers, such as liposomes or dendrimers, into inhalable formulations. To ensure optimal deep lung deposition and prevent rapid clearance, meticulous attention must be paid to the formulation's particle size, shape, and hygroscopicity. Specifically, particles with sizes between 1-5 micrometers are considered ideal for effective alveolar deposition, maximizing drug delivery to the target site [1]. In addition, the formulation must be meticulously tailored to the specific drug properties and the type of inhalation device used, whether it's a Dry Powder Inhaler (DPI), pressurized Metered-Dose Inhaler (pMDI),or nebulizer. Each device has its unique characteristics, and the formulation must be compatible with the chosen device to achieve the desired therapeutic outcomes. Among the current delivery systems, dry powder formulations have garnered significant interest due to their portability, room-temperature stability, and capability to deliver both small-molecule drugs and biologics. One notable example is the use of spray-dried microparticles produced with pullulan. These particles demonstrate excellent fine particle fractions and desirable aerodynamic properties, making them highly suitable for DPI applications. Their ability to produce consistent and uniform aerosols ensures more effective and targeted drug delivery to the lungs [2, 3]. However, designing a successful inhalation formulation is not merely a matter of selecting the right particles and device. It necessitates a deep understanding of the drug's physicochemical properties, aerosol behavior, and pulmonary physiology. This understanding is crucial for achieving accurate lung-targeted delivery, ensuring that the therapeutic agent reaches its intended site of action within the respiratory tract. Without this knowledge, the formulation may not perform optimally, leading to reduced efficacy and potential safety issues. Recently, advanced delivery systems have emerged, aiming to overcome physiological obstacles within the respiratory tract. Aerogels of biological origin, produced from natural polymers, present highly porous and lightweight structures that facilitate deep lung delivery and prolonged drug release [4]. These innovative materials offer new possibilities for enhancing existing inhalation devices and lipid-based nanocarriers, potentially leading to more effective and patient-centric

therapies. Moreover, microparticles inspired by microorganisms are being developed to replicate the structural and functional characteristics of pathogens. Core-shell designs or structures resembling pollen grains can improve mucus permeability, boost cellular absorption, and enable targeted drug administration. By mimicking nature's designs, these emerging approaches offer more efficient and adaptable solutions for treating both pulmonary and systemic conditions. These innovations hold great promise for improving patient outcomes and advancing the field of inhalation therapy. In conclusion, the field of inhalation formulations is rapidly evolving, driven by advancements in material science, device technology, and our understanding of pulmonary physiology. As researchers continue to explore new strategies for enhancing drug delivery to the lungs, the potential for inhalation therapy to improve patient outcomes will continue to grow [5]. By leveraging these innovations, we can develop more effective and tailored formulations that address the unique needs of individuals with respiratory conditions. This evolution in inhalation therapy will undoubtedly lead to improved patient care and more successful therapeutic interventions, ultimately transforming the way we treat respiratory diseases.

The article initiates with an in-depth exploration of lipid-based nanocarriers, elucidating advanced fabrication techniques like microfluidic synthesis for LNPs and novel methods such as electrostatic stabilization to enhance aerosol performance and therapeutic efficacy. It subsequently shifts focus to dry powder formulations, emphasizing state-of-the-art particulate systems developed through spray drying or employing biologically derived aerogels, ensuring precise lung targeting and tailored release profiles. Further sections delve into the integration of nanocarriers with pressurized Metered-Dose Inhalers (pMDIs) and soft-mist inhalers, addressing the challenges of incorporating fragile nanosystems, including liposomes and LNPs, into these platforms. The article concludes by detailing engineering solutions to maintain dosage accuracy and particle stability in these advanced drug delivery systems.

2. Results

2.1. Liquid formulation theory

2.1.1. Lipid nanoparticle delivery system

Recent advancements in pulmonary drug delivery have increasingly focused on lipid-based nanocarriers, such as Lipid Nanoparticles (LNPs) and liposomes, to overcome the limitations of traditional aerosol systems and enhance delivery efficiency. These nanocarriers exhibit remarkable encapsulation capacity, stability, and lung-targeted performance, making them an attractive alternative for pulmonary applications. The preparation of LNPs typically involves a microfluidic mixing technique. This method combines an organic solution containing ionizable lipids, helper lipids, cholesterol, and PEGylated lipids with an aqueous mRNA solution under acidic conditions [6]. A commonly employed formulation comprises SM-102, DSPC, cholesterol, and DMG-PEG2000 dissolved in ethanol, which is then mixed with the mRNA solution through microfluidic channels. This process results in the formation of nanoparticles with sizes ranging from 100 to 150 nanometers and encapsulation efficiencies exceeding 80% [7]. To ensure precise control over particle size and surface properties, LNPs are meticulously characterized using advanced techniques. Dynamic Light Scattering (DLS) is utilized for size distribution analysis, providing insights into the uniformity of the nanoparticles. Additionally, zeta potential analysis is performed to determine the surface charge, which is crucial for understanding their interaction with biological systems. These characterization methods confirm that the microfluidic technique yields homogeneous lipid compositions with consistent particle dimensions, ensuring optimal performance for pulmonary drug delivery applications. By leveraging these sophisticated fabrication and characterization methods, researchers can develop highly effective LNP-based formulations tailored to address the unique challenges of pulmonary delivery. These formulations have the potential to significantly improve therapeutic outcomes, ultimately transforming the landscape of pulmonary drug delivery.

Liposomal inhalation formulations are commonly created through thin-film hydration followed by extrusion, resulting in small vesicles ranging from 100 to 200 nanometers in size. These vesicles, made up of DPPC and cholesterol, can be utilized either by direct nebulization or incorporation into Soft Mist Inhalers (SMI) or pressurized Metered-Dose Inhalers (pMDI) delivery systems. Research has indicated that inhaled liposomal corticosteroids show improved lung retention and sustained release, with pharmacokinetic findings demonstrating a significant 80% reduction in clearance and a significantly prolonged half-life [4]. The performance of aerosols and the effectiveness of delivery are carefully verified through Dynamic Light Scattering (DLS) and cascade impaction testing methods, ensuring optimal results in treatment.

Utilizing a Charge-Assisted Stabilization (CAS) strategy with negatively charged DSSC-DOPE peptide-lipid conjugates significantly improves colloidal stability during nebulization. This technique boosts the percentage of intact particles post-aerosolization to above 80%, a substantial increase from the initial 17%. Cryo-TEM imaging further validates the maintenance of a uniform spherical shape and lack of contamination in the nanoparticles after nebulization [6] (Figure 1).

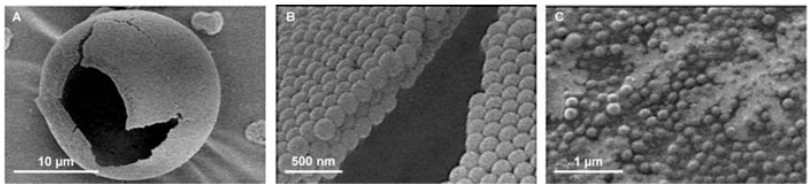

Figure 1. Cryo-TEM morphology of lipid nanoparticles (LNPs) [1]

The particles exhibit a spherical shape with a dense core and a diameter of approximately 130 nanometers,maintaining high particle integrity. Cryo-TEM imaging authenticates the true morphology of these nanoparticles.

2.1.2. LOOP platform for pulmonary mRNA delivery

Groundbreaking developments in pulmonary drug delivery have brought Lipid Nanoparticles (LNPs) to the forefront, particularly in the realm of mRNA therapeutics. A cutting-edge technology known as the LOOP platform has emerged as a game-changer, revolutionizing the functionality of LNPs through a meticulous four-stage process [6]. This process involves boosting helper lipid content, utilizing acidic dialysis, and employing excipient-facilitated nebulization. The results have been nothing short of spectacular, with significant improvements observed in nanoparticle efficiency. Specifically, the use of LOOP-optimized LNPs to administer IL-11-scFv mRNA has resulted in a remarkable reduction in pulmonary fibrosis, surpassing the outcomes achieved by conventional delivery methods. These compelling findings underscore the critical role of lipid modification and formulation strategies in addressing obstacles such as mechanical stress and endosomal escape during drug delivery. The potential for LNPs to revolutionize pulmonary drug delivery for mRNA therapeutics is tremendous, heralding a new era of research and innovation in the field.

2.2. Inhalation delivery

2.2.1. Enhancing LNP stability and immune activation

Recent advancements in Lipid Nanoparticle (LNP) engineering have led to the development of a groundbreaking technology referred to as Complexation-Associated Stability (CAS). CAS involves utilizing peptide-lipid complexes to carefully manage electrostatic forces, ensuring the stability of LNPs even during aerosolization. LNPs enhanced with CAS technology have demonstrated remarkable abilities in transferring genes through mucosal membranes and triggering strong immune responses in animal models against various strains of SARS-CoV-2 [6]. Moreover, LNPs designed to simultaneously deliver two distinct mRNA molecules have shown promising outcomes in aiding the regeneration of alveolar structures in lung fibrosis models, expanding their potential therapeutic applications beyond traditional immunization strategies [7]. This emphasizes the significance of meticulously adjusting nanoparticle properties like surface charge, size, and lipid composition to achieve precise targeting and improve immunological efficacy.

2.2.2. Nebulizers and aerosolized LNPs

Nebulizers, particularly vibrating-mesh models, are crucial in treating individuals with breathing issues like COPD or limited inhalation capacity. Researchers have recently developed Charge-Assisted Stabilized Lipid Nanoparticles (CAS-LNPs) with remarkable success [6]. By incorporating a DSSC-DOPE peptide–lipid conjugate into conventional formulations and utilizing microfluidic mixing techniques, they managed to produce uniformly sized particles around 130 nm that maintained over 80% structural integrity post-nebulization. Various advanced analysis methods like DLS and Cryo-TEM confirmed the efficiency of the CAS-LNPs [1]. In animal trials, the aerosolized CAS-LNPs have shown great promise by efficiently delivering mRNA in different animal models, resulting in significant immune responses, including protection against the Omicron variant of SARS-CoV-2 and anti-tumor effects [8]. This customized approach not only ensures consistent aerosol characteristics but also enhances the biological effectiveness of the treatment.

2.2.3. Controlled release and pharmacokinetic optimization

Pulmonary nanotherapeutics focus on achieving sustained drug release for chronic respiratory diseases. Lyotropic Liquid Crystal (LLC) systems are being explored as local depot formulations to maintain therapeutic drug levels over extended periods [7]. This structured lipid matrices have shown promise in providing prolonged release benefits. Additionally, advancements in Lipid

Nanoparticles (LNPs), including PEGylation and adjustments to lipid side chains, have improved lung retention and reduced systemic clearance. These improvements allow inhaled therapies to reach high concentrations at the target site while minimizing systemic distribution, ultimately enhancing safety and efficacy for patients. By integrating LLC systems and refined LNPs, significant progress has been made in developing effective and long-lasting pulmonary treatments that benefit individuals suffering from respiratory illnesses [7]. These innovations hold promise for the future of pulmonary medicine.

2.2.4. Dry Powder Inhalers (DPIs)

Dry Powder Inhaler (DPI) systems have become a preferred choice over lipid nanoparticle formulations for delivering medications to the lungs efficiently. While lipid nanoparticles offer good biocompatibility and gene delivery potential, their liquid form can lead to stability issues and uneven aerosol dispersion. In contrast, DPIs offer stability and effective lung deposition by breaking medication into inhalable particles through the patient's airflow. Additionally, DPIs do not rely on propellants, making them a convenient and practical option for enhancing pulmonary drug delivery. Ultimately, DPIs provide a reliable and beneficial alternative for ensuring medications reach their intended target in the lungs (Figure 2).

Figure 2. Aerodynamic behavior and deposition patterns of inhaled particles in the respiratory tract [9]

As the COVID-19 pandemic took hold in 2019, lung delivery techniques,especially Dry Powder Inhalers (DPI), gained popularity for their ability to deliver medication directly to the lungs. This method allows for precise targeting of therapeutic effects, offering a more efficient and effective way to manage respiratory conditions

Particles ranging from 1-5 μm in size are crucial for effective lung penetration. This specific range facilitates optimal delivery by enabling particles to travel deeper into the lungs through deposition processes. By ensuring medication reaches the necessary target areas, the desired outcome can be achieved. This size requirement is essential for maximizing the efficacy of pulmonary drug delivery.

Particles larger than 5 μm have the tendency to deviate from the airflow and become trapped in the mouth or trachea , a phenomenon known as inertial impaction. Due to their weight, these particles are unable to follow the airflow's path and are more likely to accumulate at branching points within the respiratory system. This underscores the significant role that particle size plays in dictating where pollutants ultimately settle within the lungs. Understanding this process is crucial in assessing the potential health impacts of airborne pollutants on respiratory health [10].

Particles between 1 and 5 μm tend to settle in the smaller airways and air sacs of the lungs,leading to potential health issues.Larger particles are more likely to deposit in the lungs the longer they remain in the airways.This natural process of gravitational sedimentation can significantly impact respiratory health and overall wellness [11].

Particles smaller than 1 μm, particularly below 0.5 μm, move randomly through Brownian Diffusion, increasing their likelihood of reaching the alveoli. Nonetheless, particles smaller than 0.5 μm remain airborne and are typically exhaled rather than settling. This movement pattern highlights the importance of size in particle deposition within the respiratory system [12].

Interception and electrostatic deposition are valuable mechanisms in improving particle retention in the respiratory tract, especially for elongated or charged particles. By utilizing these strategies, the likelihood of particles adhering to airway surfaces is significantly increased, effectively decreasing the entry of harmful contaminants into the lungs. This enhanced particle retention plays a vital role in promoting overall respiratory health and reducing the risk of respiratory issues [13].

A specialized carrier system makes use of spray-dried microparticles composed of pullulan, with a Mass Median Aerodynamic Diameter (MMAD) measuring between 2-3 μm. These microparticles, boasting a rough and porous surface as well as reduced density, are designed to enhance dispersion and lung penetration while minimizing particle adhesion. By decreasing inertial settling and increasing sedimentation, these innovative particles have been shown through various experiments to

significantly improve drug delivery efficiency. Their unique design allows them to achieve fine particle fractions of up to 68%,highlighting the remarkable advantages of their structure for targeted drug delivery purposes [5].

Moreover, preclinical investigations have revealed that once these microparticles reach the alveoli, they can break down into smaller nanoparticles, thereby enhancing cellular absorption and prolonging drug release [10].

Drug particles that enter the respiratory tract come into contact with the epithelial lining fluid, a thin layer about 10 μm thick. While highly soluble drugs dissolve quickly and diffuse rapidly through the epithelial barrier, drugs with low solubility may require controlled-release carrier systems to enhance dissolution and increase bioavailability. Improving the dissolution of poorly soluble drugs can result in more effective therapeutic results and potentially boost patient adherence to medication schedules. This highlights the importance of finding ways to increase drug solubility in order to optimize drug delivery and ultimately improve patient outcomes and treatment compliance [10].

The separation of carriers and drugs is a vital step in drug delivery systems. For example, carriers created from pullulan and leucine through spray-drying typically have a polymeric structure that encapsulates drug crystals or nanoparticles. When exposed to Extremely Low Frequency (ELF) waves, the water-soluble carrier breaks down, releasing the drug components it contains .Microparticles made from pullulan and trehalose ,for instance, swell and dissolve gradually, resulting in a sustained drug release lasting approximately 60 minutes. This slow release is a stark contrast to standard formulations ,which release the drug rapidly in just 2 minutes. The dissociation of the carrier-drug combination is therefore essential in regulating the drug release rate [11].

Alveolar absorption is a vital component in drug delivery, as it facilitates the passage of molecules from the alveolar epithelium into the bloodstream. While carrier materials are usually eliminated through natural mechanisms like mucociliary action or engulfment by macrophages, certain carriers such as chitosan-based matrices have the ability to prolong drug retention in the lungs. This resistance to phagocytosis and promotion of sustained release of nanoparticles allows for improved drug delivery and effectiveness in targeted lung treatments. The importance of alveolar absorption and retention in pharmaceutical applications cannot be overstated, highlighting the significant impact it has on enhancing drug delivery outcomes [14].

Recent advancements in nanoparticle technology have led to the creation of microparticles that, upon hydration, break down into smaller nanoparticles. These smaller particles, ranging in size from 100 to 200 nm, have shown remarkable abilities to penetrate cells more effectively, leading to improved drug delivery efficiency. By utilizing processes like endocytosis or transcytosis, these nanoparticles are able to easily enter cells, offering a new and innovative method for enhancing drug delivery systems. This groundbreaking approach holds significant potential for revolutionizing the field of pharmaceuticals [15] (Figure 3).

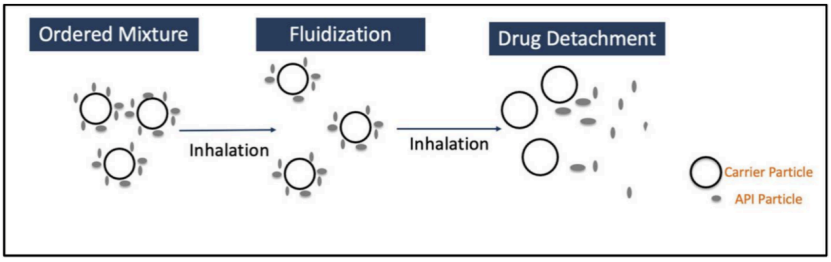

Figure 3. Working principle and airflow-driven dispersion mechanism of dry powder inhalers (DPIs) [10]

2.2.5. Metered-Dose and Soft-Mist Inhalers (MDIs and SMIs)

The development of Metered-Dose Inhalers (MDIs) and Soft-Mist Inhalers (SMIs) has significantly transformed the landscape of drug delivery for respiratory diseases. These innovative devices have successfully overcome the limitations of dry powder inhalers by incorporating nanoformulation strategies to ensure consistent dosing regardless of patient inspiratory flow. MDIs and SMIs stand out as indispensable tools for managing respiratory conditions due to their ability to accurately and swiftly deliver medication directly into the lungs. Recently, there has been a surge of interest in harnessing the potential of lipid-based drug carriers, such as liposomes and Lipid Nanoparticles (LNPs), in combination with MDIs and SMIs [16]. These carriers have the remarkable capability to encapsulate a wide range of therapeutic agents, which not only enhances drug stability but also improves cellular uptake. Moreover, their phospholipid composition makes them highly compatible with the natural surfactants present in the lungs, resulting in outstanding biocompatibility and prolonged drug retention in lung tissues. The integration of lipid-based nanocarriers with MDIs and SMIs represents an exciting breakthrough in the realm of respiratory drug delivery. By leveraging these advanced carriers, researchers are able to elevate the effectiveness and efficiency of inhalation therapy, ultimately providing significant benefits to individuals suffering from respiratory conditions [16].

Inhalers have revolutionized the way specialized drug formulations are delivered, allowing for direct administration of high concentrations of medication to the exact area that needs treatment. This targeted approach not only maximizes the effectiveness of the medication but also minimizes overall exposure throughout the body. By avoiding the first-pass metabolism, lipid-based

formulations have proven to be highly effective in providing treatment precisely where it is needed most, showing immense potential in improving treatment outcomes and patient adherence [17]. Metered Dose Inhalers (MDIs) have emerged as a cost-effective and user-friendly option that promotes good patient compliance. On the other hand, Soft Mist Inhalers (SMIs) like the Respimat device offer a propellant-free alternative that ensures a fine and consistent mist for optimal lung deposition, eliminating the need for complex inhalation techniques. A prime example of this innovative technology is Arikayce, a liposomal amikacin inhalation suspension that effectively targets challenging lung infections by delivering antibiotic-loaded liposomes directly to the respiratory tract. Furthermore, recent advancements in inhaled Lipid Nanoparticle (LNP) systems have shown promising results in administering cutting-edge therapies, such as mRNA-based treatments for pulmonary fibrosis [18]. This highlights the immense clinical potential of aerosolized nanomedicine for innovative and targeted medical interventions.

Incorporating liposomes or LNPs into pressurized MDIs and SMIs holds great promise for revolutionizing pulmonary drug delivery. However, technical challenges must be overcome to maximize the potential benefits of these advanced lipid-based delivery systems [16]. Pressurized MDIs, in particular, face obstacles due to the presence of hydrophobic propellants and the high shear stress generated during actuation. These conditions can cause damage to the lipid vesicles, resulting in clumping or breakage that compromises the stability and effectiveness of the drugs. Consequently, the clinical advancement of liposomal MDIs has been hindered, with no liposomal inhaler currently being commercialized. While SMIs offer a propellant-free alternative that is gentler on sensitive formulations, they require long-term stability of the nanoformulation in aqueous environments and come with higher manufacturing costs [19]. Additionally, the risk of nanoparticles aggregating presents challenges, as larger particles may not effectively reach deep lung regions or may be cleared by the body, reducing therapeutic efficacy. Despite these barriers, researchers are actively seeking solutions such as protective coatings for liposomes to enhance formulation stability. The ongoing exploration of integrating user-friendly inhaler devices with advanced lipid-based delivery systems remains a promising frontier in pulmonary medicine. This integration has the potential to improve targeted drug delivery, enhance patient compliance, and ultimately lead to superior outcomes in respiratory care. Through diligent research and innovative solutions, the field of pulmonary drug delivery is poised to achieve significant advancements in the near future.

2.3. Biological aerogels and microbial-inspired particles in inhaled formulations

2.3.1. Biological aergel for pulmonary drug delivery

Researchers are continuously exploring new methods to improve drug loading capacity and control release kinetics. One promising approach involves the use of highly porous and biomimetic carriers, such as biological aerogels and microbial-inspired particles. These innovative delivery systems combine structural efficiency with biological functionality, effectively addressing challenges related to drug distribution and cellular absorption. Biological aerogels, derived from natural polymers like alginate, chitosan, cellulose, and proteins, possess unique characteristics such as extremely low density, high porosity, and a large surface area. These properties make them ideal for applications in pulmonary drug delivery [20]. With aerogel microparticles typically ranging from 1 to 5 μm in Mass Median Aerodynamic Diameter (MMAD), they can effectively reach deep into the lungs and avoid mucociliary clearance due to their porous structure and lightweight nature.

Aerogels made from alginate and chitosan using advanced production methods demonstrate great potential in drug delivery applications. Alginate-based aerogels, manufactured through spray gelation and supercritical drying, are capable of effectively encapsulating and releasing drugs like ketoprofen and methylprednisolone when exposed to lung lining fluid [21]. On the other hand, chitosan-derived aerogel particles, created through a combination of gelation, spray drying, and supercritical drying techniques, possess a high specific surface area of around 254 m^2/g, significant porosity of about 99%,and the ability to transport amines like clomipramine to the brain through nasal administration. These findings suggest promising uses in pulmonary delivery systems, highlighting the versatility and potential impact of these aerogels in the field of drug delivery [22].

Aerogel particles, when inhaled, offer promising possibilities for improved drug delivery and treatment within the respiratory system. These particles possess a significant surface area that enables rapid absorption of lung fluid, facilitating the release and dissolution of drugs. The porous structure of aerogels also supports sustained drug release, preventing quick clearance [23]. Made from biocompatible ingredients such as alginate, chitosan, and proteins, they reduce immune responses and aid in biodegradation. With their ability to penetrate deep into the lungs, regulate drug delivery, and work well with the pulmonary system, biological aerogels stand out as an innovative carrier system. Overall, aerogels hold tremendous potential for enhancing respiratory treatment outcomes.

2.3.2. Microbial particles for pulmonary drug delivery

Cutting-edge advancements in drug delivery systems are transforming the way medications are administered, particularly in the context of respiratory infections. Innovations such as shell-core architectures, elongated shapes, and charged surfaces are being utilized to enhance mucosal penetration and prevent phagocytosis [23]. By mimicking the behavior of viruses and bacteria, these novel designs effectively facilitate intracellular uptake. For example, particles modeled after pollen with shell-core structures

capitalize on Brownian motion to efficiently target the alveoli, replicating the aerodynamics of natural pathogens. Moreover, the integration of antimicrobial peptides and antibiotics, like the SET-M33 peptide, into PEGylated PLGA nanoparticles has shown great potential in combatting alveolar infections [24]. These tailored drug delivery systems can effectively penetrate mucosal biofilms, undergo endocytosis, and provide lasting antibacterial effects with reduced toxicity. This Trojan-horse approach showcases the promise of personalized drug delivery systems in addressing respiratory infections [25].

Innovative microbial-inspired platforms utilize low-density porous structures, such as aerogel matrices resembling spores. When paired with antibiotics or peptides, the aerogel carrier enables controlled dissolution and targeted release. The nanoparticles mimic pathogens' cell entry kinetics, promising the development of efficient drug delivery systems that provide precise and effective treatment options [26].

Aerogels, when infused with antimicrobial compounds such as cinnamaldehyde, have the potential to imitate microbial processes and serve as efficient carriers for antibiotics. This innovative approach has displayed encouraging results in providing controlled release and effective distribution of antibacterial substances within the lungs. Studies have revealed the success of mesoporous silica aerogels loaded with these agents in combatting various infections [27].

Innovative methods like spray freeze-drying and supercritical fluid processing can transform porous particles to have lightweight densities and aerodynamic qualities resembling harmful pathogens. These particles can now reach deep into the lungs for precise drug delivery and controlled release, enhancing treatment effectiveness [26].

2.3.3. Physical stability and storage considerations

Physical stability is a critical factor in the formulation of dry powder inhalers, as it plays a significant role in maintaining the performance of these inhalable carriers in various storage and humid conditions. It is essential to ensure that the structural and physicochemical integrity of spray-dried powders, known for their amorphous nature, is preserved to prevent moisture-related degradation like recrystallization, particle aggregation, and changes in aerodynamic properties under high humidity [28]. For instance, research has shown that amorphous ciprofloxacin formulations experience a notable decrease in fine particle fraction when stored at 55% relative humidity, primarily due to structural recrystallization. Therefore, developing a deep understanding of and improving the physical stability of these formulations is crucial to ensure consistent and reliable aerosol performance throughout the product's shelf life.

The incorporation of suitable excipient coatings, such as L-leucine at concentrations ranging from 10% to 40% w/w, has been found to significantly improve the resistance of powder formulations to moisture. By forming a protective crystalline layer, these coatings effectively reduce surface area and minimize particle adhesion, leading to enhanced overall performance. Research has demonstrated that powder formulations containing approximately 30-40% leucine exhibit optimal aerosol performance even when exposed to humidity levels of 60-75% RH.L-leucine plays a vital role in migrating to the particle surface during spray drying, creating a hydrophobic shell that decreases interparticle cohesion and moisture absorption [29]. This protective crystalline layer serves to prevent amorphous particles from recrystallizing in humid conditions, ensuring consistent aerosol flowability and aerodynamic performance throughout storage.

Mannitol and trehalose are vital hydrophilic excipients that play essential roles in enhancing stability in formulations. Mannitol serves as a filler agent due to its semi-crystalline nature, while trehalose preserves biomolecular integrity through its glass-forming properties. However, when used independently, these excipients tend to absorb moisture more readily. By combining trehalose and mannitol, formulations exhibit improved powder flowability and long-term stability. The synergistic effect of combining both excipients elevates overall performance, fortifying the formulation against moisture. Formulations that incorporate a blend of trehalose and mannitol outshine those utilizing either excipient alone, ensuring superior stability and efficacy over time [30].

Recent research has revealed the effectiveness of freeze-drying combined with cryoprotectants like sucrose or trehalose in maintaining the particle size and encapsulation efficiency of Lipid Nanoparticle (LNP) formulations, even when stored at 2-8 °C or at room temperature [31, 32]. Furthermore, utilizing spray-drying with excipients such as leucine has proven successful in enhancing dispersibility and preventing particle aggregation in LNP powders. This breakthrough in technology offers promising solutions for the long-term storage and preservation of LNPs, guaranteeing their efficacy and performance over time. These innovative methods provide a reliable way to ensure the stability and functionality of LNPs, even after extended periods of storage, thus advancing the field of nanoparticle research [33].

The structural integrity of bioaerogel s is greatly affected by ambient humidity levels. When chitosan and alginate aerogels are dried using supercritical methods, they can maintain their high porosity and surface area in dry environments. However, if the relative humidity exceeds 65%, there is a risk of pore collapse and significant shrinkage within a short period of time [34]. To address this issue, recent advancements have been made with hybrid materials like alginate–chitosan composites. These composites improve durability by preserving surface charge and reducing aggregation during extended storage [35]. By storing these aerogels in desiccated capsules, they can retain their structural characteristics and drug delivery capabilities. This makes them suitable for use in Dry Powder Inhaler (DPI) formulations, showing promising potential in the medical field.

2.4. Application of inhaler therapies

Inhalation therapy has seen remarkable progress due to the harmonious combination of stable formulations, enhanced aerodynamic performance, and innovative device design. This progress has resulted in a significant improvement in the efficiency of pulmonary drug delivery and has expanded the potential treatment options available to patients. Dry powder Inhalers (DPIs) have emerged as a particularly successful method for administering respiratory medications, providing patients with easy-to-use dosing schedules that help improve adherence to treatment. Originally developed for managing asthma and COPD, DPIs have since evolved to cater to a wide range of therapeutic uses by ensuring precise and effective drug delivery to the lungs. The following examples highlight the diverse pharmacological approaches made possible by this groundbreaking inhalation technology.

2.4.1. Trelegy ellipta

Introducing a innovative triple-combination therapy for COPD and asthma, containing fluticasone furoate, umeclidinium, and vilanterol, promising round-the-clock symptom relief. With its unique design of two separate blister strips for each medication, this inhaler ensures accurate dosing. This convenient once-daily treatment option significantly enhances the lives of individuals suffering from respiratory conditions, providing seamless and effective relief [36].

2.4.2. Treprostinil inhalation powder (YUTREPIA)

In 2025, a groundbreaking treatment was introduced for Pulmonary Arterial Hypertension (PAH) and Pulmonary Hypertension linked to Interstitial Lung Disease (PH-ILD).The cutting-edge Dry Powder Inhaler (DPI) employs state-of-the-art PRINT® technology to administer a prostacyclin analog directly to the lungs, leading to better tolerance and increased exercise capacity. This therapy holds great potential for enhancing the health outcomes of individuals affected by these ailments [37].

2.4.3. Frevecitinib inhalation therapy

A new dry powder treatment for asthma patients, undergoing Phase 2b clinical trials, has shown promising results. This treatment specifically targets airway inflammation in patients who do not respond to traditional maintenance therapies. Early findings suggest the treatment is effective, with minimal absorption into the body, making it a potential option for precise inhaled immunomodulatory therapy [38].

2.4.4. Quattrii DPI platform

Quattrii, a state-of-the-art DPI device, is transforming the administration of high-dose biologics like mRNA therapies. With an impressive lung delivery efficiency of over 70%, Quattrii surpasses traditional inhalers with added carrier particles for enhanced comfort during use. This innovative technology has the potential to revolutionize the treatment of pulmonary diseases and may even impact lung-related cancers. The future of respiratory healthcare looks bright with the groundbreaking capabilities of Quattrii leading the way towards more effective and convenient therapy options.

2.4.5. Custom triple combination (FP/SX/TB DPI)

A new dry powder formulation combining fluticasone propionate, salmeterol xinafoate, and tiotropium bromide was created by filling powdered ingredients into capsules during preclinical tests. Animal studies indicated that this DPI shared comparable pharmacokinetic and deposition characteristics with existing commercial products, hinting at potential bioequivalence. This breakthrough formulation showcases a hopeful outlook for advancements in pharmaceutical research and development [39].

2.4.6. LNP combined with dual mRNAs for the treatment of pulmonary fibrosis

Scientists have developed an innovative Lipid Nanoparticle (LNP) system to deliver two crucial mRNAs for treating Idiopathic Pulmonary Fibrosis (IPF). This breakthrough technique targets cytochrome b5 reductase 3 and BMP4,showing promise in reversing fibrosis in mouse models. The inhalable LNPs boast consistent aerosol properties and high transfection rates in the lungs, while avoiding systemic toxicity. Studies indicate low accumulation in the liver, making it a safer option for long-term inhalation therapy for chronic fibrotic conditions. This groundbreaking approach offers hope for the future treatment of IPF and similar diseases, paving the way for new possibilities in combating these debilitating conditions [40].

2.4.7. The CAS-LNP system delivers mRNA vaccines

A groundbreaking platform known as Charge-Assisted Stabilized Lipid Nanoparticles (CAS-LNPs) has been created to safeguard mRNA from physical harm while undergoing nebulization. By integrating peptide-lipid conjugates (DSSC-DOPE) into conventional LNP compositions, the CAS-LNPs enhance electrostatic bonds, guaranteeing enhanced particle durability. Following aerosol administration, these CAS-LNPs retained more than 80% of their initial composition and size uniformity. This pioneering method represents a significant advancement in maintaining mRNA integrity during delivery procedures, offering great promise for future applications [41].

2.4.8. Alginates-based bio-gel is used for inhalation of corticosteroid delivery

Novel alginate-based aerogels produced using supercritical drying have been successfully utilized to encapsulate beclomethasone dipropionate for more effective pulmonary delivery. The porous particles, measuring approximately 2 micrometers, were found to have a low bulk density, enabling targeted deposition in the alveolar regions of the lungs. In vitro experiments indicated a consistent and extended release of the drug over an 8-hour period. The large surface area of the aerogel structure allowed for a higher drug payload and prevented powder aggregation, ultimately improving the reliability and shelf life of Dry Powder Inhalers (DPIs). This innovative method shows great potential in enhancing the delivery of pharmaceuticals to patients with respiratory conditions.

3. Conclusion

The evolution of pulmonary drug delivery methods has been a focal point of extensive research efforts, spanning from traditional inhalation techniques to cutting-edge nanoparticle-based systems. Through a thorough examination of different delivery methods such as Dry Powder Inhalers (DPIs), Metered-Dose Inhalers (MDIs), and Soft-Mist Inhalers (SMIs), it is evident that particle engineering plays a crucial role in optimizing lung deposition efficiency. Various factors including aerodynamic size, moisture absorption, and surface properties are carefully analyzed to enhance drug delivery efficacy. Additionally, the integration of liquid formulations underscores the significance of achieving chemical compatibility between active pharmaceutical ingredients and excipients. Whether in the form of stable emulsions, liposomal suspensions, or nanoparticle dispersions, these liquid formulations serve as the basis for customized delivery mechanisms that impact drug solubility, dissolution rates, and bioavailability. Innovative approaches like spray drying are utilized to develop personalized delivery systems that aim to improve drug effectiveness and ultimately enhance patient outcomes.

New drug delivery methods are pushing boundaries with the use of bio-inspired aerogels and dry powder formulations derived from microbes. Mimicking structures found in nature, such as bacterial core-shell designs and fungal spores, these systems provide advantages like enhanced porosity, controlled drug release, and better distribution in the lungs. When combined with antibiotics or immune-modulating peptides, these innovative approaches offer powerful antimicrobial effects and personalized pharmacokinetic profiles. The future of pharmaceutical delivery technology looks bright with these exciting advancements on the horizon.

The last portion of the paper discusses key considerations in designing Dry Powder Inhalers (DPIs), focusing on the critical role of selecting excipients like leucine and mannitol to improve aerosol stability and maintain effectiveness. It underscores the significance of storing DPIs in humidity-resistant conditions and the proper techniques for dispersing dry powder to ensure optimal delivery. Case studies of successful DPI treatments, including Trelegy, Yutrepia, and CAS-LNP mRNA vaccines, are analyzed to showcase the diverse formulation approaches tailored to address different respiratory issues while guaranteeing both effectiveness and durability.

In the near future, significant progress is expected in the field of pulmonary therapeutics through the innovative use of inhalable formulations and Lipid Nanoparticle (LNP) delivery systems. Cutting-edge techniques in particle engineering, including precision-controlled spray drying and 3D-printed particulate systems, are set to revolutionize the creation of inhalable powders by enhancing deposition efficiency and allowing for customizable release profiles. Furthermore, next-generation LNPs are anticipated to incorporate new lipid variants and surface modifications to improve biological barrier resistance, enable better mucus penetration, and target specific lung cell populations. A crucial advancement involves the conversion of liquid nanoparticle dispersions into stable dry powder forms through methods like lyophilization or spray-freeze drying. This breakthrough combines the convenience and portability of Dry Powder Inhalers (DPIs) with the therapeutic flexibility of nanomedicine, paving the way for a promising future in pulmonary therapeutics.

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