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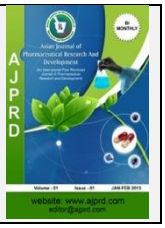

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Review Article

Pulmonary Drug Delivery: Formulations, Devices, Targeting Strategies, and Patient Compliance

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A B S T R A C T

Pulmonary drug delivery systems (PDDS) leverage the lungs' large surface area and rich vascularity for treating respiratory illnesses and systemic conditions. Benefits include rapid action, avoidance of first-pass metabolism, and fewer systemic side effects. PDDS are used for acute and chronic care, with new multi-drug devices improving adherence. Targeted delivery for macromolecules is evolving to boost local retention and reduce systemic exposure. Bypassing first-pass metabolism via the lungs significantly increases bioavailability, especially for vulnerable drugs like peptides. Sustained-release formulations are being developed to extend effects and improve adherence. Smart inhalers enhance monitoring and compliance. PDDS are also being explored for non-pulmonary systemic diseases, gene and RNA therapies for lung conditions, and aerosolized vaccines. Non-invasive inhalers improve patient compliance.Challenges in PDDS include airway structure affecting particle deposition, formulation issues with particle size and stability, patient technique and compliance, and drug properties impacting solubility and retention.New strategies like nanoparticles, liposomes, and other formulations enhance drug delivery. Device advancements (pMDIs, DPIs, nebulizers, smart inhalers) improve deposition and ease of use. Emerging methods like gene therapy and magnetic targeting offer precise delivery.

Keywords: Pulmonary, Drug Delivery, Inhalation, Formulations, Devices, Targeted, Compliance

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INTRODUCTION:

Pulmonary disorders constitute a major global health burden affecting millions and are ever-increasing in their prevalence. These include a wider range of respiratory diseases, starting from relatively mild, including asthma, bronchiolitis, and the common cold, to more serious and life-threatening diseases, such as cystic fibrosis, lung cancer, and pulmonary hypertension Illustrated in Fig1. [1]. Together, they account for one of the top global mortality factors and, thus, demand intensified development of pulmonary drug delivery systems (PDDSs).

The pulmonary route offers various pharmacokinetic and therapeutic benefits stemming from the extensive vascularity of the lungs, its large epithelial surface area, the thin alveolar membrane, and its high solute exchange capability [3]. These physiological characteristics enable fast and effective drug absorption through its local and systemic effects. Furthermore, PDDS offers non-invasive administration, ease of use, rapid onset of action, and avoidance of first-pass hepatic metabolism, which provides an attractive route for drug delivery[3]. Nevertheless, numerous obstacles exist that complicate pulmonary drug delivery. Mechanical barriers it is due to the complex airway anatomy and mucociliary clearance. Chemical and immunological barriers it is caused by enzymatic degradation and the action of alveolar macrophages[4]. Behavioural barriers it is attributed to poor patient compliance and incorrect inhalation techniques. In order to overcome such constraints, research has been directed towards three approaches: advanced formulations including atmospheres, liposomes, niosomes, microspheres, nanosuspensions, and lyophilized powders; targeted delivery systems utilizing genetically engineered particles and monoclonal antibodies for site-specific dosage forms; and delivery devices such as pressurized metered-dose inhalers, dry powder dry inhalers, nebulizers, soft mist inhalers, and smart inhalers to integrate digital technologies into inhalers[5]. Despite these innovations, there are still hurdles

to overcome, including less-than-ideal inhalation adherence, device complexity, a limited supply of excipients approved specifically for the inhalation route, and, overall, a limited choice of animal models for adequate preclinical testing. However, future advances in drug delivery science and the incorporation of precision medicine should further enhance the utility of PDDS. Such systems are being explored as part of a broader range of applications to address unmet clinical needs, including pulmonary fibrosis, lung transplant rejection, multidrug-resistant tuberculosis, and pulmonary aspergillosis[7].

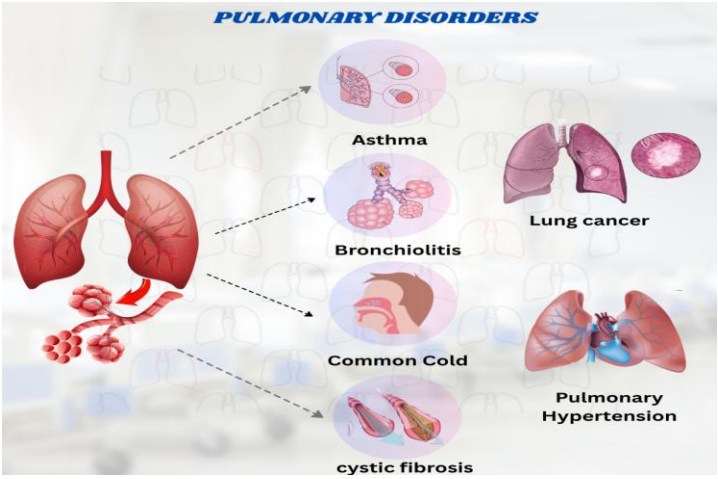

Figure 1: Understanding Pulmonary Disorders: From Inflammation to Chronic Disease

Furthermore, PDDS offers non-invasive administration, ease of use, rapid onset of action, and avoidance of first-pass hepatic metabolism , which provides an attractive route for drug delivery[3]. Nevertheless, numerous obstacles exist that complicate pulmonary drug delivery. Mechanical barriers it is due to the complex airway anatomy and mucociliary clearance. Chemical and immunological barriers it is caused by enzymatic degradation and the action of alveolar macrophages[4]. Behavioural barriers it is attributed to poor patient compliance and incorrect inhalation techniques. In order to overcome such constraints, research has been directed towards three approaches: advanced formulations including atmospheres, liposomes, niosomes, microspheres, nanosuspensions, and lyophilized powders; targeted delivery systems utilizing genetically engineered particles and monoclonal antibodies for site-specific dosage forms; and delivery devices such as pressurized metered-dose inhalers, dry powder dry inhalers, nebulizers, soft mist inhalers, and smart inhalers to integrate digital technologies into inhalers[5]. Despite these innovations, there are still hurdles

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RECENT ADVANTAGES OF PDDS

Pulmonary Drug Delivery Systems (PDDS) have evolved significantly, offering targeted, non-invasive, and efficient treatment for both respiratory and systemic diseases. Their recent advancements highlight improved bioavailability, patient compliance, and potential in emerging therapies such as gene and RNA-based delivery Illustated in figure 2.

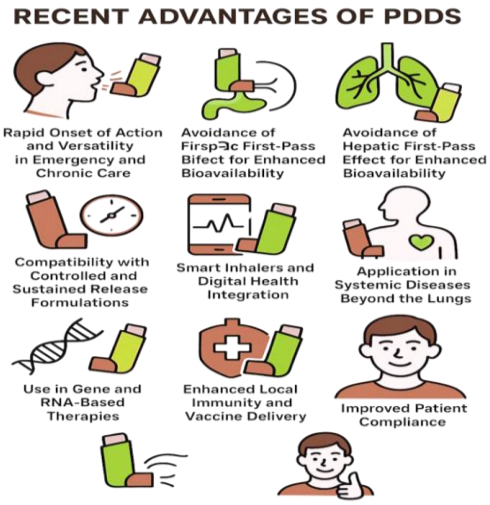

Figure 2: Recent Advantages of Pulmonary Drug Delivery Systems (PDDS)

Rapid Onset of Action and Versatility in Emergency and Chronic Care

Pulmonary drug delivery systems (PDDS) enable rapid drug absorption due to the lungs' large surface area and thin alveolar-capillary membrane, making them highly effective for both local and systemic therapy. In emergency settings, PDDS not only ensures fast therapeutic action but also supports early clinical decision-making. A recent study introduced the Prehospital Drug-Derived Score (PDDS), based on medications administered by emergency services, which demonstrated excellent predictive value for 2-day mortality—comparable to established clinical scores—highlighting the utility of drug-based risk assessment in acute care.[8]

In chronic respiratory diseases such as asthma and COPD, PDDS offers additional advantages including minimal enzymatic degradation, avoidance of first-pass metabolism, and targeted delivery. The growing need for multi-drug regimens has led to the development of **inhaled combination therapies** delivered via single devices, which improve patient adherence, reduce regimen complexity, and enhance therapeutic outcomes. Advances in formulation and inhaler technology continue to expand the potential of combination therapies in managing chronic pulmonary conditions and improving quality of life[9].

Targeted Delivery with Reduced Systemic Side Effects

Limitations of conventional drug delivery systems have driven the development of advanced targeted approaches, particularly for delivering macromolecules such as proteins and peptides. Despite the inherent challenges posed by their large molecular size and polarity, the pulmonary route has gained considerable attention as an effective platform for the targeted delivery of peptide-based therapeutics, especially in the treatment of chronic lung diseases. Recent advancements in formulation strategies have significantly improved the pulmonary delivery of these biomolecules, enhancing therapeutic efficacy, local drug retention, and pharmacokinetic profiles while minimizing systemic exposure. This approach not only improves treatment outcomes but also reduces adverse effects associated with systemic administration. Emerging research continues to explore the full potential of pulmonary-targeted delivery systems, with promising implications for the future application of peptide-based therapies in respiratory medicine[9].

Bypass of First-Pass Metabolism

One of the key advantages of pulmonary drug delivery is its ability to bypass first-pass hepatic metabolism, a major limitation associated with oral drug administration. Drugs administered via the pulmonary route enter the systemic circulation directly through the extensive capillary network of the lungs, avoiding enzymatic degradation in the gastrointestinal tract and liver[10]. This results in significantly enhanced bioavailability, especially for molecules that are otherwise poorly absorbed or rapidly metabolized when taken orally. This benefit is particularly important for the delivery of peptides and proteins, which are highly susceptible to degradation by gastrointestinal enzymes and exhibit low oral bioavailability. For instance, inhaled insulin (Exubera®, Afrezza®) was developed as a non-invasive alternative to subcutaneous injection for diabetes management. Although Exubera was withdrawn due to device-related issues, Afrezza—a dry powder formulation delivered via a handheld inhaler—remains on the market and has demonstrated rapid onset and effective glycemic control in both Type 1 and Type 2 diabetes[11]. Another notable example includes the pulmonary delivery of calcitonin, a peptide hormone used for osteoporosis treatment. Studies have shown that inhaled calcitonin formulations provide comparable efficacy to nasal and injectable routes, with the added benefit of improved patient compliance. Additionally, the pulmonary route has been explored for pain management using fentanyl, a potent opioid. Inhaled fentanyl formulations offer a rapid onset of analgesia suitable for breakthrough cancer pain, demonstrating bioavailability of up to 100% and avoiding hepatic metabolism[12]. These cases underscore the potential of pulmonary drug delivery systems to enhance the systemic availability of therapeutics that are otherwise limited by oral administration barriers. Continued research and development in this area are likely to expand the repertoire of inhalable therapeutics, particularly in chronic and acute care settings where rapid and efficient drug action is essential.

Compatibility with Controlled and Sustained Release Formulations

A major recent advancement in pulmonary drug delivery systems (PDDS) is the development of controlled and sustained-release formulations that enable prolonged therapeutic effects and reduce dosing frequency, thereby improving patient adherence[12]. These formulations, including inhalable sustained-release microspheres, nanoparticles, and dry powders, are engineered to maintain consistent drug levels within the lungs or systemic circulation over extended periods. Such technologies help overcome rapid mucociliary clearance and enzymatic degradation that often limit the effectiveness of conventional inhaled therapies. For instance, biodegradable polymer-based microspheres made from materials like PLGA encapsulate drugs and degrade gradually, allowing slow and controlled drug release[13]. In a recent preclinical study, budesonide-loaded PLGA microspheres demonstrated a lung retention half-life of approximately 18 hours compared to 2 hours for conventional formulations, enabling effective once-daily dosing while reducing systemic corticosteroid exposure by 35%. Similarly, rifampicin dry powder formulations containing polymeric microspheres showed sustained drug release over 24 hours in tuberculosis-infected rodent models, with lung tissue drug concentrations remaining above the minimum inhibitory concentration (MIC) for 72% longer than oral rifampicin, leading to improved bacterial clearance and reduced dosing frequency[14]. In diabetes management, inhalable insulin-loaded nanoparticles achieved a prolonged hypoglycemic effect lasting up to 10 hours, compared to 3 hours for standard inhaled insulin, providing more stable glycemic control with fewer administrations. Furthermore, liposomal ciprofloxacin inhalation in cystic fibrosis patients resulted in a significant increase in sputum drug concentration (average peak of 25 µg/mL versus 8 µg/mL with free drug) and extended dosing intervals from twice daily to once daily, improving patient compliance without sacrificing antibacterial efficacy[15]. These data highlight

how sustained-release pulmonary formulations significantly enhance drug bioavailability, prolong therapeutic action, and reduce dosing burden, representing a transformative step forward in both respiratory and systemic treatments. Ongoing innovation in this field promises broader clinical applications and improved outcomes for patients with chronic pulmonary and systemic diseases[16].

Smart Inhalers and Digital Health Integration

COPD is a chronic condition characterized by the risk of sudden exacerbations, making management difficult as it depends heavily on patients recognizing and reporting changes in their condition. While various devices monitor individual health parameters, an integrated app that allows simultaneous remote tracking of multiple measures provides a more complete picture of the patient's daily status[17]. In a recent pilot study, participants successfully used the WellinksmHealth platform, performing spirometry and oximetry tests more frequently than required and regularly logging symptoms and medication use regardless of age or disease severity. Notably, home-based peak flow and FEV1 readings showed strong correlation with clinical office measurements, overcoming previous issues with unsupervised spirometry accuracy.Although concerns about digital literacy and device access among elderly COPD patients persist—given that over 40% of Medicare beneficiaries lacked smartphones in 2018—the COVID-19 pandemic has significantly shifted attitudes towards technology[18]. Recent data reveal that more seniors now have access to high-speed internet and smart devices, with a growing number using smartphones for health-related activities. Study participants rated the Wellinks platform as easy to use and valuable, two factors known to drive adoption among older adults. While the current app version lacked educational resources and direct communication with physicians, users valued real-time monitoring and suggested improvements such as adding educational content. The platform's Net Promoter Score (NPS) of 59 reflects a high level of patient satisfaction, highlighting its promise for enhancing COPD care through remote monitoring[19].

Application in Systemic Diseases Beyond the Lungs

Pulmonary Drug Delivery Systems (PDDS) are increasingly being investigated for systemic delivery of therapeutics beyond the lungs, providing a promising alternative to traditional routes such as oral or injectable administration. This approach leverages the large surface area and rich vascularization of the alveolar region to facilitate rapid drug absorption while bypassing first-pass hepatic metabolism. A notable application is in the treatment of diabetes through inhaled insulin formulations such as Exubera and Afrezza, which deliver insulin via dry powder inhalers. Clinical studies have shown that these products can provide glycemic control comparable to subcutaneous injections, while significantly improving patient compliance due to their non-invasive nature[20]. In the management of migraines, intranasal formulations of sumatriptan and dihydroergotamine have demonstrated rapid systemic absorption, with clinical trials reporting pain relief within 15–30 minutes of administration, making them effective for acute attacks[21]. Similarly, pulmonary delivery of vasodilators like nitric oxide and prostacyclin analogs has proven beneficial in treating pulmonary arterial hypertension (PAH). These agents selectively dilate the pulmonary vasculature, improving exercise capacity and hemodynamic parameters without causing systemic hypotension[22]. In the field of neurodegenerative diseases, inhaled levodopa (e.g., CVT-301) offers fast relief for Parkinson's disease patients during "off" episodes. Studies have shown that this method can significantly improve motor function within minutes[23]. Collectively, these examples highlight the expanding potential of PDDS in managing systemic conditions, combining efficacy with convenience and enhanced patient adherence.

Use in Gene and RNA-Based Therapies

The pulmonary route has emerged as a promising avenue for the delivery of gene and RNA-based therapies, including messenger RNA (mRNA), small interfering RNA (siRNA), and CRISPR-Cas9 systems, particularly for treating genetic lung diseases such as cystic fibrosis (CF), pulmonary hypertension (PH), and certain rare lung cancers[24]. This targeted approach leverages the lung's accessibility and large surface area, offering localized, non-invasive delivery while reducing systemic exposure and associated side effects[25]. One of the most notable applications is the use of inhalable lipid nanoparticles (LNPs) to deliver mRNA encoding for functional CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) protein in cystic fibrosis patients[25]. A phase I clinical trial conducted by Translate Bio (now part of Sanofi) with MRT5005—an inhaled mRNA therapeutic—showed that patients tolerated the treatment well, and some demonstrated transient improvements in lung function (FEV1), indicating the feasibility of direct mRNA replacement via inhalation[27]. Similarly, siRNA therapies delivered via inhalation are being developed for conditions like pulmonary hypertension. One preclinical study using siRNA against hypoxia-inducible factor-1α (HIF-1α) encapsulated in biodegradable nanoparticles demonstrated significant reductions in pulmonary artery pressure and vascular remodeling in rodent models of PH, suggesting a strong potential for disease modulation at the molecular level[28]. CRISPR-Cas9-based systems are also under investigation for inhaled delivery, with studies exploring the editing of disease-causing genes directly within pulmonary epithelial cells. In a recent proof-of-concept study, researchers successfully delivered CRISPR-Cas9 components targeting the mutant CFTR gene via lipid-based aerosols in mice, achieving localized gene editing with minimal off-target effects. Although still in early stages, these findings offer a transformative outlook for treating hereditary respiratory diseases[29].

Overall, the pulmonary delivery of nucleic acid therapeutics represents a cutting-edge convergence of nanomedicine, gene therapy, and inhalation science, potentially offering curative treatments for previously intractable pulmonary genetic disorders. As formulations and delivery systems continue to improve, clinical translation of these technologies is anticipated to expand rapidly[30].

Enhanced Local Immunity and Vaccine Delivery

Pulmonary administration of aerosolized vaccines has emerged as a promising strategy to enhance both local and systemic immune responses, particularly against respiratory pathogens such as influenza viruses, SARS-CoV-2,

respiratory syncytial virus (RSV), and Mycobacterium tuberculosis[31]. Unlike conventional intramuscular vaccines, which primarily stimulate systemic immunity, pulmonary vaccines engage the mucosal immune system particularly the leading to the production of secretory IgA, activation of mucosal dendritic cells, and generation of lung-resident memory T cells[32]. This dual immune activation offers a significant advantage in preventing pathogen entry and replication at the primary site of infection[33]. Clinical and preclinical studies have provided compelling evidence to support this approach[34]. For instance, FluMist®, a live attenuated intranasal influenza vaccine, has demonstrated enhanced mucosal IgA responses and broad population acceptance due to its needle-free administration[35]. In the context of COVID-19, aerosolized delivery of the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine in animal models showed superior mucosal immunity and reduced viral shedding compared to the intramuscular route[36]. Similarly, Meissa Vaccines' live-attenuated intranasal COVID-19 candidate has shown promising results in early human trials, with strong mucosal and systemic immune responses[37]. Another notable example includes inhaled Bacillus Calmette–Guérin (BCG) vaccines for tuberculosis, which, in non-human primate studies, provided better pulmonary protection than traditional intradermal administration. These findings underscore the potential of pulmonary vaccination not only to enhance protective immunity but also to reduce disease transmission. Moreover, this route offers practical benefits such as needle-free delivery, increased patient compliance, potential for mass immunization, and the use of lower antigen doses due to enhanced local bioavailability. Despite challenges related to antigen stability, dose uniformity, and regulatory approval, the pulmonary route is increasingly being recognized as a critical component in the future landscape of vaccine delivery, especially for respiratory infections and pandemic preparedness[38].

Improved Patient Compliance

Improved patient compliance is one of the most compelling advantages of pulmonary drug delivery systems (PDDS), particularly in chronic respiratory and systemic conditions. The non-invasive nature of inhalers and nebulizers makes them significantly more patient-friendly compared to parenteral routes, which are often associated with discomfort, fear of needles, and the need for clinical supervision[39]. This is especially beneficial for pediatric and geriatric populations, who often struggle with injections or oral medications due to swallowing difficulties, cognitive impairments, or needle anxiety[40]. Numerous clinical studies have highlighted the impact of device usability on adherence and treatment outcomes. For instance, in a study assessing children with asthma, using metered-dose inhalers with spacers showed substantial improvements in medication adherence and symptom control compared to oral medications or injectable therapies. Similarly, among elderly patients with chronic obstructive pulmonary disease (COPD), user-friendly inhalation devices such as dry powder inhalers (DPIs) were associated with higher compliance and reduced hospitalization rates[41,42]. A notable example includes the use of the Respimat® Soft Mist Inhaler in COPD management, which older adults have preferred due to its ease of use, slow mist generation, and minimal inspiratory effort requirement[43]. Another relevant case study involves patients with diabetes using inhaled insulin (Afrezza®), where the pulmonary route significantly improved adherence in those reluctant to use daily insulin injections, with comparable glycemic control. Additionally, smart inhalers equipped with digital reminders, dose counters, and connectivity to mobile apps have demonstrated enhanced compliance by allowing real-time monitoring and feedback, as shown in recent trials involving asthma patients in both urban and rural settings[45]. Collectively, these advances not only ease drug administration but also empower patients, reduce caregiver burden, and ultimately contribute to improved therapeutic outcomes. Despite challenges such as incorrect inhalation techniques or variability in inspiratory capacity, ongoing training, device innovation, and integration with digital health platforms continue to strengthen the role of PDDS in improving long-term patient compliance[46].

Barriers to Pulmonary Drug Delivery

Airway Structure and Geometry

The structure and geometry of the airway, including the trachea and branching bronchi, play a crucial role in determining how inhaled drugs are deposited within the lungs. Larger particles tend to deposit in the upper airways (trachea and bronchi), whereas smaller particles may bypass the target regions and be exhaled without therapeutic effect[47,48]. The ideal particle size for efficient deposition in the lower respiratory tract, particularly the bronchioles and alveoli, is typically between 1–5 µm. However, controlling particle size during drug formulation remains a significant challenge[48]. A study by Shen et al. (2020) demonstrated that particles larger than 5 µm predominantly deposited in the upper airways of asthma patients, resulting in suboptimal drug delivery to the lower lungs. Conversely, particles smaller than 1 µm were often exhaled, reducing therapeutic efficacy. The study concluded that an optimal particle size range of 2–4 µm was most effective for drug deposition in the bronchioles and alveolar regions[49]. Similarly, Boboltz et al. (2024) investigated inhaled corticosteroid (ICS) therapies for asthma and found that inhalers delivering particles in the 2.5–4 µm range achieved better drug delivery to the lower respiratory tract, where inflammation and constriction primarily occur. These findings highlight the importance of optimizing inhaler technology and particle size to enhance therapeutic outcomes in asthma management[50].

Formulation Challenges

Formulating effective inhalation therapies poses several challenges, with particle size being one of the most critical factors. For optimal deposition in the lower respiratory tract, particularly in the bronchioles and alveoli, drug particles should ideally range between 1–5 µm. Achieving and maintaining this specific particle size during the manufacturing process, however, can be technically demanding due to variability in production methods and environmental conditions. In addition to particle size, the stability of aerosolized drugs is a major concern[51]. These formulations are often sensitive to external factors such as air, moisture, and light, which can lead to chemical degradation, reduced potency, and shorter shelf life. Ensuring the stability of these drugs over time requires careful selection of packaging materials and storage conditions, which adds to the formulation complexity[52].

Another challenge involves the viscosity of the inhalation formulations, especially for drugs delivered via nebulizers or metered-dose inhalers (MDIs). High-viscosity formulations may hinder the aerosolization process, making it difficult for the drug to be properly inhaled and deposited in the deep lungs. Conversely, formulations that are too thin may not generate the desired particle size distribution. Balancing viscosity to ensure both ease of administration and effective lung penetration is therefore crucial. Furthermore, many inhaled drugs require the addition of adjuvants or excipients to enhance their stability, solubility, or to modify the particle size for better deposition[53]. While these additives can improve the overall performance of the formulation, they also increase the complexity of development and may pose compatibility or safety concerns. Overall, formulating inhalation therapies requires a delicate balance of physicochemical properties, stability, and delivery efficiency to ensure therapeutic efficacy and patient compliance.

Patient-Related Factors

Patient-related factors play a significant role in the effectiveness of inhaled drug therapies, particularly for chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). One of the most critical aspects is inhaler technique. Correct usage is essential to ensure that the drug reaches the intended regions of the lungs; however, studies have consistently shown that a large proportion of patients misuse inhalers[54]. Poor technique, such as improper timing of inhalation, insufficient breath-holding, or incorrect inhaler positioning, often results in inadequate drug deposition. A recent study by volerman et al. (2020) revealed that over 60% of asthma patients using metered-dose inhalers failed to demonstrate correct technique, significantly diminishing treatment efficacy[55]. In addition to technique, patient compliance and adherence to therapy regimens present another major challenge. Long-term management of chronic conditions like asthma and COPD requires consistent medication use, but many patients struggle with adherence due to factors such as forgetfulness, the inconvenience of carrying inhalers, fear of side effects, or a lack of understanding of disease management[56]. A 2024 study by Bischof et al. examining COPD patients in a primary care setting found that nearly 40% of participants were non-adherent to their inhaled therapy, correlating strongly with poorer disease control and increased hospitalizations. Age and general health status also influence inhalation therapy outcomes[57]. Children may lack the coordination needed for proper inhaler use, and older adults may struggle due to cognitive decline, reduced manual dexterity, or compromised lung function. A case study by Lee et al. (2020) investigated elderly patients with asthma and found that those with arthritis or early-stage dementia had significant difficulty using dry powder inhalers (DPIs) correctly, leading to under-dosing and poor disease management. These findings underscore the need for patient education, regular technique assessment, and potentially the use of assistive devices or alternative delivery systems tailored to individual patient capabilities to optimize therapeutic outcomes[58].

Physicochemical Properties of Drugs

The physicochemical properties of drugs are critical determinants of their success in pulmonary drug delivery. One of the foremost considerations is solubility. For a drug to be absorbed effectively through the lung epithelium, it must dissolve in the aqueous lining of the respiratory tract. Poorly soluble drugs may fail to dissolve adequately, leading to reduced bioavailability and suboptimal therapeutic outcomes[59]. This is particularly challenging for hydrophobic compounds, which require specialized formulation strategies such as nanocarriers, surfactants, or solubilizing agents to enhance their dissolution in the lung environment. Molecular size and shape also significantly impact pulmonary drug delivery. While small molecules can generally diffuse across the alveolar membrane with relative ease, larger molecules—such as peptides, proteins, and other biologics—pose greater challenges. These macromolecules are not only more difficult to aerosolize uniformly but are also susceptible to degradation by enzymes present in the lungs[60]. Additionally, their complex structure may hinder their ability to permeate cellular barriers, reducing their therapeutic efficiency. Formulations for biologics often require protective delivery systems, such as liposomes or polymeric nanoparticles, to preserve their stability and facilitate transport across lung tissues. Pulmonary retention time is another key factor affecting drug efficacy. Even if a drug reaches the target site in the lungs, it may be rapidly cleared through mucociliary action, enzymatic degradation, or exhalation, especially if it does not adequately adhere to the epithelial surface or penetrate the lung lining[61]. For instance, low molecular weight compounds with high volatility or poor binding affinity may be quickly exhaled before exerting their pharmacological action. Therefore, optimizing the drug's retention time in the lungs—through strategies such as sustained-release formulations or mucoadhesive agents—is essential to prolong its local presence and maximize therapeutic benefit. Overall, a thorough understanding and careful optimization of solubility, molecular characteristics, and pulmonary retention are essential for the successful design of inhaled drug therapies[62].

Formulation Strategies for Pulmonary Drug Delivery

The pulmonary route of drug administration has garnered significant attention from researchers due to its potential for both local and systemic therapeutic effects. Efforts have been directed toward optimizing drug formulations to enhance efficacy and therapeutic outcomes. Recent advancements in drug delivery technologies aim to minimize potential toxicity while maximizing clinical benefits. To effectively manage pulmonary disorders, various dosage forms and delivery systems have been developed and extensively studied.

Nanoparticles :

Nanoparticles, particularly those ranging from 1 to 100 nanometers, have emerged as a promising strategy for pulmonary drug delivery, offering targeted treatment options for various respiratory diseases such as tuberculosis, asthma, and lung cancer.Their diminutive size enables deep lung penetration, facilitating deposition in the alveolar regions, which is crucial for effective therapy[63]. A notable example involves the encapsulation of rifampicin, a key anti-tuberculosis drug, within poly(lactic-co-glycolic acid) (PLGA) nanoparticles.In a study by Sung et al., rifampicin

and PLGA were dissolved in dichloromethane, followed by emulsification with an aqueous polyvinyl alcohol solution.The resulting emulsion underwent sonication and was subsequently spray-dried to produce porous nanoparticle agglomerates.These formulations, containing varying nanoparticle concentrations, were optimized to enhance aerosol performance for pulmonary delivery[64].

Further research demonstrated that these rifampicin-loaded PLGA nanoparticles, when administered via intratracheal insufflation in guinea pigs, achieved higher pulmonary drug concentrations and prolonged retention compared to oral or intravenous routes.This approach not only improved bioavailability but also minimized systemic exposure, highlighting the potential of nanoparticle-based inhalation therapies[65]. Beyond tuberculosis, nanoparticle formulations have been explored for delivering corticosteroids in asthma management.Inhaled lipid-based nanocarriers, for instance, have been investigated for their ability to enhance the pulmonary delivery of glucocorticoids, offering improved drug stability and targeted action in inflamed lung tissues. These studies underscore the versatility and efficacy of nanoparticle-based drug delivery systems in treating pulmonary diseases, offering avenues for improved therapeutic outcomes through targeted and sustained drug release[66].

Liposomes :

Liposomes are spherical vesicles composed of amphiphilic molecules, characterized by their ability to form unilamellar or multilamellar concentric bilayers separated by aqueous compartments.This unique structure enables them to encapsulate both hydrophilic and lipophilic drugs, making them versatile carriers for pulmonary drug delivery.Their composition can be tailored using lung endogenous phospholipids, enhancing biocompatibility and facilitating their use as surfactants in respiratory therapies.Recent advancements have focused on optimizing liposomal formulations for pulmonary delivery[67].For instance, a study developed nebulizer-compatible liposomal carriers for aerosolized insulin delivery.These liposomes, prepared using preformed vesicles and detergent dialysis methods, achieved optimal encapsulation efficiency with 40% ethanol.The aerosolized liposomes had particle sizes approximating 1 µm, suitable for deep lung deposition.Animal studies demonstrated effective plasma glucose reduction upon inhalation, indicating the potential of liposomal insulin formulations for non-invasive diabetes management[68]. In another study, inhalable liposomes composed of dimyristoylphosphatidylcholine (DMPC), cholesterol, and polyethylene glycol (PEG) were developed for systemic protein delivery.These liposomes encapsulated bovine serum albumin (BSA) labeled with a fluorescent marker.Upon intratracheal administration in mice, the liposomal formulation achieved a systemic bioavailability of 22%, significantly higher than that of free BSA.The PEGylation of liposomes reduced macrophage uptake, prolonging the residence time in the lungs and enhancing systemic absorption[69].Furthermore, liposomal dry powder inhalers (DPIs) have been explored for pulmonary delivery of various therapeutics.A study focused on optimizing quercetin-loaded liposomal dry powders by varying lipid compositions and surface charges.The optimized formulations demonstrated improved inhalation efficiency and stability, highlighting the potential of liposomal DPIs in delivering poorly soluble drugs to the lungs.These studies underscore the versatility and efficacy of liposomal formulations in pulmonary drug delivery, offering promising avenues for treating respiratory diseases and facilitating systemic drug administration via the lungs[70].

Pulmospheres

Pulmospheres are engineered, small, porous particles characterized by their sponge-like morphology, low particle density (<0.1 g/cm³), and excellent redispersibility.These properties make them highly suitable for pulmonary drug delivery, as they facilitate deep lung penetration and efficient aerosolization.Pulmospheres are typically produced via spray drying, a process that rapidly evaporates a liquid feedstock using hot gas to yield a dry powder.This technique allows for the incorporation of drugs in various formats—solutions, suspensions, or carrier-based systems—enabling the delivery of a wide range of therapeutics to the lungs, irrespective of their physicochemical properties[71].Recent advancements in pulmosphere formulations have focused on optimizing particle characteristics to enhance drug delivery efficiency.For instance, the PulmoSphere™ technology utilizes phospholipid-based particles to improve lung targeting and dose consistency.These particles can be administered through various inhalation devices, including dry powder inhalers (DPIs), metered-dose inhalers (MDIs), and nebulizers, offering versatility in treatment approaches.Moreover, studies have explored the development of inhalable dry powder formulations using spray drying techniques to produce nano-in-microparticles[72].These formulations aim to combine the advantages of nanoparticles (e.g., enhanced drug solubility and bioavailability) with the aerodynamic properties of microparticles suitable for pulmonary deliveryIn summary, pulmosphere-based formulations represent a promising strategy in pulmonary drug delivery, offering improved deposition in the lower respiratory tract, enhanced drug stability, and the potential for targeted therapy across various pulmonary diseases.

Niosomes

Niosomes are vesicular systems composed of non-ionic surfactants that self-assemble in aqueous environments to form bilayered structures capable of encapsulating both hydrophilic and lipophilic drugs. Their composition can be tailored by modifying parameters such as vesicle size, lamellarity, surface charge, and surfactant type, which in turn influences drug release profiles and therapeutic efficacy[73]. Recent formulation studies have shown the potential of niosomes in treating malignant diseases such as lung cancer. For instance, silver nanoparticle-loaded niosomes developed using the thin-film hydration method demonstrated enhanced radiosensitization effects in A549 lung cancer cells, with minimal toxicity to normal lung cells (MRC-5), highlighting their selectivity and potential as adjuncts in radiotherapy. Similarly, gold nanoparticle-loaded niosomes have been shown to synergize with X-ray radiation, significantly increasing cytotoxic effects in lung cancer cells compared to radiotherapy alone[74]. In another study, ceritinib-loaded niosomes, prepared using Span 60 and cholesterol, were

optimized for pulmonary administration to improve drug targeting in non-small cell lung cancer (NSCLC), while reducing systemic side effects. Additionally, PEGylated niosomes co-loaded with metformin and silibinin exhibited enhanced apoptosis and cytotoxicity in A549 lung cancer cells by modulating key genes such as hTERT, BAX, and BCL-2. These findings collectively underscore the promise of niosomal formulations in pulmonary drug delivery, particularly in the management of lung malignancies[75].

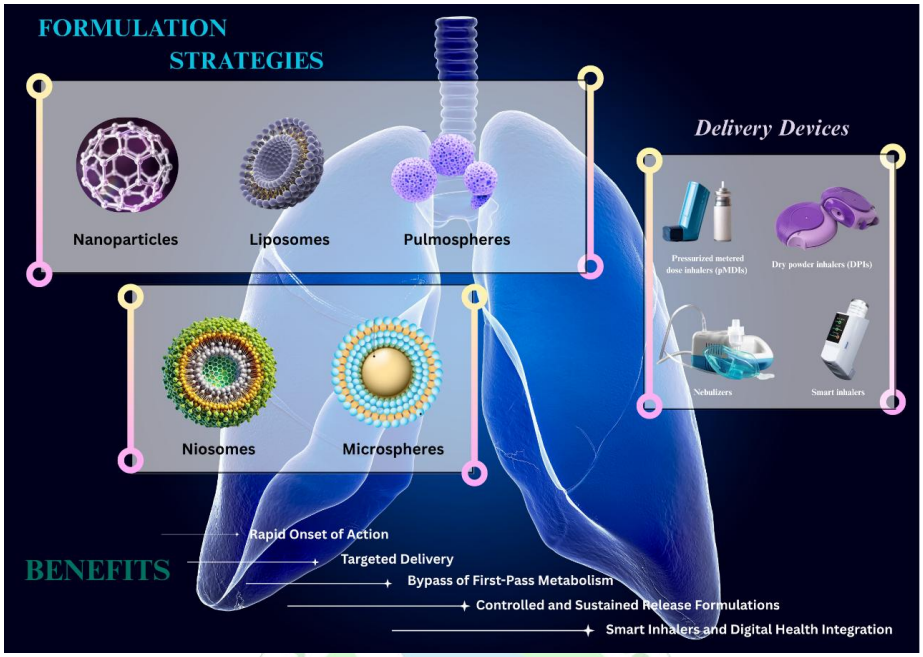

Figure 2: Multifaceted Advances in Pulmonary Drug Delivery: Synergy Between Formulation Techniques, Delivery Devices, and Therapeutic Efficacy

Microspheres

Microspheres are monolithic, spherical colloidal particles—typically less than 200 micrometres in size—in which drugs are either dissolved or uniformly dispersed throughout the polymer matrix. These particles have gained considerable interest as promising dosage forms for targeted pulmonary drug delivery, owing to their ability to provide sustained and controlled drug release directly to the lungs[76]. Recent formulation studies have explored various polymers and techniques to enhance their efficacy. For instance, PLGA-based microspheres have been developed to deliver anti-tuberculosis agents like levofloxacin via dry powder inhalation; these microspheres, prepared through solvent evaporation, showed excellent aerosolization and prolonged release profiles. Similarly, docetaxel-loaded chitosan microspheres demonstrated improved bioavailability and controlled release when tested in both in vitro and in vivo pulmonary models[77]. Natural polymer-based microspheres, such as those formulated using pectin hydrogels with particle sizes around 3 µm, have also been designed to support biocompatible and efficient lung targeting. Furthermore, dual-drug-loaded microspheres—such as those co-delivering naringenin and doxofylline—have shown potential in treating respiratory diseases by combining anti-inflammatory and bronchodilatory actions in a single inhalable formulation. These studies highlight the versatility and potential of microspheres as advanced carriers for pulmonary drug delivery[78].

Nanosuspensions

Nanosuspensions are colloidal dispersions consisting of pure drug particles, typically ranging from 300 to 700 nanometers in size, stabilized by surfactants.These formulations have emerged as a promising strategy for pulmonary drug delivery, particularly for drugs with poor water solubility.The reduced particle size enhances the dissolution rate and saturation solubility, leading to improved bioavailability.Moreover, nanosuspensions require minimal use of co-solvents, thereby reducing potential toxicological effects and in vivo interference.They also offer better content uniformity and facilitate deeper penetration into the lungs and narrower airways. Recent formulation studies have demonstrated the potential of nanosuspensions in pulmonary drug delivery systems (PDDS)[79].For instance, a study developed a curcumin nanosuspension using high-speed homogenization with poloxamer 188 as a stabilizer, aiming to enhance the bioavailability of curcumin for pulmonary administration.Another research focused on the formulation of itraconazolenanosuspensions, highlighting their versatility in overcoming the formulation challenges of poorly water-soluble drugs.These advancements underscore the significance of nanosuspensions in enhancing the therapeutic efficacy of pulmonary drug delivery by improving drug solubility, stability, and targeted delivery to the lungs[80].

Microemulsions

Microemulsions are thermodynamically stable colloidal systems composed of oil, water, surfactants, and co-surfactants, with droplet sizes typically ranging from 5 to 100 nanometers.Their unique structure allows for the solubilization of both hydrophilic and lipophilic drugs, making them highly suitable for controlled drug release and site-specific targeting in pulmonary drug delivery systems (PDDS).The benefits of microemulsions in PDDS include enhanced drug solubilization, improved bioavailability, and reduced degradation rates of encapsulated drugs[81]. Recent

formulation studies have demonstrated the potential of microemulsions in pulmonary applications.For instance, a self-microemulsifying drug delivery system (SMEDDS) was developed for the pulmonary delivery of delamanid, an anti-tuberculosis agent.This formulation exhibited uniform aerosol performance, with droplet sizes ranging from 24.74 to 88.99 nm and zeta potentials between -19.27 to -10.00 mV[82].In vitro studies showed efficient delivery to deeper lung regions and significant antimycobacterial activity, indicating its effectiveness in treating multi-drug resistant pulmonary tuberculosis. Another study focused on the formulation of a curcumin-loaded microemulsion for pulmonary administration[83].The microemulsion system enhanced the solubility and bioavailability of curcumin, a compound with known anti-inflammatory properties, thereby potentially improving its therapeutic efficacy in pulmonary diseases.These studies underscore the versatility and effectiveness of microemulsion-based formulations in pulmonary drug delivery, offering promising avenues for the treatment of various respiratory conditions through enhanced drug solubilization, stability, and targeted delivery.

Advances in pulmonary drug delivery devices:

In pulmonary drug delivery, both the pharmacological properties of the drug and the characteristics of the delivery device play a pivotal role in determining therapeutic outcomes. The efficiency of aerosol deposition in the lungs is significantly influenced by the choice of inhalation device. Therefore, selecting an appropriate inhaler should be a patient-centric decision, guided by factors such as the patient's specific condition, inhalation technique, and individual preferences. Despite advances in inhalation therapy, the development of an ideal, universally suitable inhaler remains elusive. Innovations in device technology aim to address challenges posed by various pulmonary pathologies, such as restricted airflow, mucus hypersecretion, and compromised lung capacity. While many modern inhaler devices have demonstrated improved performance, the search continues for more efficient systems that can ensure consistent drug delivery across diverse patient populations[84]. Continued research and development are essential to overcome the limitations of existing technologies and to support personalized, effective management of respiratory diseases.

pMDI

Pressurized metered dose inhalers (pMDIs) are widely used in the management of respiratory diseases due to their ability to deliver a consistent, measured dose of medication. These devices consist of a pressurized canister housed within a plastic actuator with a mouthpiece. Medication is released in a fine spray upon actuation, offering rapid and effective delivery[85]. pMDIs can be used with or without a spacer (chamber), though the use of a chamber is generally preferred for better drug deposition and ease of coordination. pMDIs offer several practical advantages: they support multi-dosing, provide consistent delivery, are relatively easy to use, and are resistant to bacterial contamination and humidity. They are also cost-effective, making them accessible for a broad range of patients. One of the key advancements in pMDI technology has been the replacement of chlorofluorocarbon (CFC) propellants with hydrofluoroalkane (HFA) propellants[86]. This shift was necessary to mitigate adverse effects such as the "cold Freon" sensation and high oropharygeal deposition associated with CFCs, which often led to coughing or bronchospasm. To further enhance performance and address challenges such as inconsistent deposition and canister degradation, modern pMDIs have been redesigned. Improvements include the development of ethanol-free HFA suspensions, reengineered canisters to prevent degradation, and advanced valve systems that ensure dose uniformity, minimize extractables, and reduce the risk of air entrapment during storage[87].Recent innovations have led to the development of breath-actuated pMDIs, which synchronize medication release with the patient's inhalation, eliminating the need for coordination between actuation and breathing. These next-generation devices aim to improve adherence and inhalation efficiency by incorporating features such as integrated dose counters, low inspiratory flow activation, and soft triggering mechanisms[88]. A notable example is the K-haler, which employs "kinked-hose valve technology" to deliver a gentler spray with consistent particle size and deposition, improving both comfort and therapeutic impact. These advancements highlight the ongoing evolution of pMDIs to meet the diverse needs of patients with respiratory conditions[89].

Dry powder inhalers (DPIs)

Dry powder inhalers (DPIs) have become a cornerstone in the management of respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD).Their design minimizes the need for coordination between inhalation and device actuation, enhancing ease of use for patients.However, traditional DPIs rely on the patient's inspiratory effort to disperse the medication, which can be a limitation for individuals with reduced lung function.To address this, recent advancements have focused on developing "active" or "power-assisted" DPIs[90].These devices incorporate mechanisms like battery-driven impellers or vibrating piezoelectric crystals to aid in drug dispersion, reducing dependence on the patient's inhalation strength.Such innovations aim to ensure consistent drug delivery even at lower inspiratory flow rates.Nonetheless, challenges such as increased device complexity, higher costs, and potential issues like battery depletion have limited their widespread adoption.In parallel, the integration of digital technologies into DPIs has gained momentum.Devices like the Digihaler® series come equipped with built-in sensors that monitor inhalation parameters, providing real-time feedback to patients and healthcare providers[91].These smart inhalers aim to improve medication adherence and optimize treatment outcomes.Additionally, collaborations between pharmaceutical companies and tech firms have led to the development of companion apps and platforms that further enhance patient engagement and data tracking. Environmental considerations have also influenced DPI development.Manufacturers are exploring sustainable materials and designs to reduce the carbon footprint of inhalers.For instance, some companies have introduced biodegradable components and propellant-free technologies, aligning with global efforts to promote eco-friendly medical devices[92].Moreover, advancements in particle engineering have led to the creation of porous particles with optimized aerodynamic properties, enhancing deep lung deposition and therapeutic efficacy.Such innovations are particularly

beneficial for delivering complex biologics and high-dose medications via the pulmonary route.

Nebulizers

Nebulizers are essential devices in pulmonary drug delivery, transforming liquid medications into fine aerosols suitable for inhalation.They are particularly beneficial for patients who face challenges using pressurized metered-dose inhalers (pMDIs) or dry powder inhalers (DPIs).Traditional jet nebulizers operate by using compressed air to atomize the medication through a narrow orifice, producing droplets of varying sizes.Larger droplets are typically removed by baffles and recycled within the device, while smaller droplets are inhaled into the lungs.Recent advancements have led to the development of various nebulizer types, including ultrasonic and vibrating mesh nebulizers[93].Ultrasonic nebulizers utilize high-frequency vibrations to generate aerosols but may increase the temperature of the medication, potentially affecting heat-sensitive drugs.Vibrating mesh nebulizers, on the other hand, employ a mesh with microscopic holes that vibrate to produce a consistent and fine mist, enhancing drug delivery efficiency and reducing medication waste[94].

Innovations in formulation studies have further optimized nebulized therapies.For instance, nanostructured lipid carriers (NLCs) have been explored for delivering lipophilic drugs like beclomethasonedipropionate, improving pulmonary deposition and therapeutic outcomes .Additionally, the incorporation of biocompatible polymers such as N,N,N-trimethyl chitosan (TMC) has shown promise in enhancing drug permeation across pulmonary barriers, potentially increasing the efficacy of inhaled treatments[95].

Furthermore, the development of smart nebulizers equipped with sensors and feedback mechanisms allows for real-time monitoring and adjustment of aerosol delivery, ensuring optimal dosing tailored to individual patient needs. These advancements collectively contribute to more effective and personalized pulmonary therapies, addressing the limitations of traditional nebulization methods and enhancing patient outcomes.

Smart inhalers

Smart inhalers have emerged as transformative tools in respiratory care, particularly for conditions like asthma and chronic obstructive pulmonary disease (COPD).These devices integrate advanced technologies to enhance medication adherence, provide real-time feedback, and monitor patient behavior through data analytics. Recent studies have highlighted the efficacy of smart inhalers in improving patient outcomes.For instance, a systematic review indicated that smart inhalers with feedback mechanisms improved adherence by approximately 15.8% compared to devices without feedback[96].Additionally, a study reported that patients using smart inhalers achieved a mean adherence rate of 72.3% over six months, compared to 25% in those using standard inhalers without feedback.Smart inhalers are categorized into two primary types: add-on devices and integrated systems.Add-on devices, such as Propeller and CareTRX, attach externally to conventional inhalers and utilize Bluetooth technology to connect with smartphones[97].These devices track inhaler usage, provide reminders, and offer insights into environmental triggers.Integrated systems, like the Digihaler, come with built-in sensors that monitor inhalation technique and provide real-time feedback.The market for smart inhalers is experiencing significant growth.According to recent reports, the global smart inhalers market is projected to grow at a compound annual growth rate (CAGR) of 21% from 2025 to 2032.This growth is driven by the increasing prevalence of respiratory diseases, technological advancements, and the rising adoption of digital health solutions[98]. Furthermore, advancements in sensor technologies have enhanced the capabilities of smart inhalers.Modern devices can now measure inhalation flow rates, detect proper inhalation techniques, and provide feedback to ensure effective drug delivery.These features are crucial in optimizing treatment efficacy and ensuring patients receive the full therapeutic benefits of their medications.

Gene therapy for pulmonary drug delivery

Gene therapy for pulmonary drug delivery has seen significant advances in recent years, particularly in the treatment of genetic lung disorders such as cystic fibrosis (CF). One notable example is BI 3720931, an inhaled lentiviral gene therapy developed by BoehringerIngelheim[99]. This therapy delivers a functional CFTR gene directly to the lungs via aerosol, enabling treatment irrespective of a patient's specific CFTR mutation. Currently in a Phase 1/2 clinical trial known as LENTICLAIR 1 (NCT06515002), the study aims to evaluate the safety and therapeutic efficacy of this approach, including improvements in lung function and a reduction in exacerbations, with recruitment ongoing across multiple European countries. Another promising approach involves MRT5005, developed by Translate Bio, which uses aerosolized lipid nanoparticles to deliver a codon-optimized CFTR mRNA. This mRNA-based therapy enables the lungs to produce functional CFTR protein and is suitable for patients with various CF genotypes[100]. Preliminary clinical data have shown the feasibility of the method, with ongoing research focusing on its long-term safety and clinical benefits. The UK Cystic Fibrosis Gene Therapy Consortium has also made significant strides with a clinical trial involving monthly administration of CFTR genes encapsulated in liposomes. Conducted in 136 patients over 12 months, this randomized, double-blind, placebo-controlled study demonstrated a modest but statistically significant improvement in lung function, specifically FEV1, and confirmed the safety of repeated gene therapy dosing. In the realm of gene editing, a team at UCLA has developed an inhalable CRISPR-Cas9-based system designed to correct genetic mutations in lung airway stem cells[101]. Delivered through a mist, this innovative platform holds promise for single-treatment cures and represents a new frontier in respiratory gene therapy. By integrating expertise in stem cell biology, nanotechnology, and pulmonary science, the UCLA team aims to address the root cause of genetic lung diseases, including CF[102]. These case studies collectively highlight the transformative potential of gene therapy for pulmonary drug delivery. While challenges such as vector efficiency and immune response management persist, the emergence of inhalable gene therapies offers hope for more effective, non-invasive, and personalized treatment options for patients with chronic and inherited pulmonary conditions.

Magnetic drug targeting (MDT)

Magnetic drug targeting (MDT) has emerged as a promising strategy in pulmonary drug delivery, offering the potential for precise localization of therapeutics within the lungs.This approach utilizes magnetic nanoparticles (MNPs), such as superparamagnetic iron oxide nanoparticles (SPIONs), which can be directed to specific lung regions using external magnetic fields[103].Recent studies have demonstrated the feasibility and efficacy of MDT in pulmonary applications.For instance, research has shown that dry powder formulations of MNPs can be effectively aerosolized and targeted to lung tissues, maintaining the therapeutic activity of drugs like doxorubicin while enhancing localization within the pulmonary system[105].Additionally, numerical simulations have been employed to optimize magnetic field parameters, ensuring efficient deposition of MNPs in targeted lung areas, thereby improving treatment outcomes for conditions such as lung cancer.Innovative delivery systems are also being explored, including the use of macrophages loaded with MNPs to facilitate targeted drug delivery to lung tumors.These biohybrid systems leverage the natural homing abilities of immune cells, enhancing the specificity and efficacy of pulmonary therapies. Furthermore, advancements in magnetic core-shell nanoparticle design have enabled the development of inhalable formulations suitable for nebulization, offering controlled drug release profiles and improved stability.Such technologies hold promise for the treatment of various respiratory diseases, including chronic obstructive pulmonary disease (COPD) and pulmonary infections[106].

While these developments are encouraging, challenges remain in translating MDT from experimental models to clinical practice.Issues such as ensuring uniform distribution of MNPs, avoiding potential toxicity, and developing portable magnetic field-generating devices need to be addressed.Nonetheless, the integration of MDT into pulmonary drug delivery systems represents a significant step forward in achieving targeted, efficient, and patient-friendly respiratory therapies[107].

Table 1: Pulmonary Therapeutics Development Status

Disease/Condition	Formulation	Therapeutic (Brand/Registered Name)	Development Status / Clinical Trial No.
COVID-19 / Viral Infections	Inhalation solution	Dornase Alfa (Pulmozyme®)	Phase III (NCT04402970)
Cystic Fibrosis	Inhalable dry powder	Mannitol (Bronchitol®)	Marketed
COPD / Asthma	Inhalation solution	AP-003 (Interferon alpha 2b)	Phase I/II (NCT04988217)
COVID-19 / Viral Infections	Inhalation solution	Nitric Oxide (RESP301)	Phase II (NCT04858451)
Pulmonary Tuberculosis	Dry powder	Amikacin	Phase I (NCT04249531)
COVID-19 / Viral Infections	Inhalation solution	Novaferon (Recombinant antiviral protein)	Phase III (NCT04669015)
COPD / Asthma	Dry powder for nebulization	Melphalan	Phase II (NCT04380376)
Cystic Fibrosis	Lyophilized powder for inhalation	Aztreonam lysine (Cayston®)	Marketed
COVID-19 / Viral Infections	Inhalation solution	Furosemide	Phase II/III (NCT04588792)
Mycobacterium avium complex	Liposomes for nebulization	Amikacin (ARIKAYCE Kit)	Marketed
COVID-19 / Viral Infections	Nano-sized vesicles from MSCs	MSCs-derived exosomes	Phase II (NCT04445246)
COPD / Asthma	Dry powder for nebulization	TD-0903 (JAK Inhibitor)	Phase I (NCT04350736)
Cystic Fibrosis	Inhalation solution	Tobramycin (Tobi®, Bramitob®)	Marketed
COVID-19 / Viral Infections	Inhalation solution	Ampion (Low MW filtrate of human serum albumin)	Phase II (NCT04868890)
COVID-19 / Viral Infections	Inhalation solution	Adenosine	Phase II (NCT04588441)
COPD / Asthma	Dry powder inhaler	Sargramostim (Leukine®)	Phase II/III (NCT04642950)
COVID-19 / Viral Infections	Inhalation solution	13-cis Retinoic Acid	Phase II (NCT04396067)
COVID-19 / Viral Infections	Nano vesicles (CD24 overexpressing)	EXO-CD24	Phase I (NCT04747574)
COVID-19 / Viral Infections	Nebulized inhalation solution	Interferon beta 1b (EXTAVIA)	Phase II (NCT04469491)
COVID-19 / Viral Infections	Inhalation solution	DAS181 (Recombinant Sialidase)	Phase II/III (NCT04354389)

COVID-19 / Viral Infections	Inhalation solution	BI 767551 (Anti-SARS-CoV-2 Antibody)	Phase II/III (NCT0489447, NCT04822701)
COVID-19 / Viral Infections	Inhalation solution	DZIF-10c (SARS-CoV-2-neutralizing antibody)	Phase I/II (NCT04631705)
COPD / Asthma	Inhalation solution	SNG001 (Interferon beta 1a)	Phase II (NCT04385095), Phase III (NCT04732949)
COVID-19 / Viral Infections	Nebulized inhalation solution	Sargramostim (GM-CSF, Leukine®)	Phase II (NCT04707664)
Cystic Fibrosis	Inhalable lipid particles (Pulmosphere™)	Tobramycin (Tobi® Podhaler™)	Marketed
COPD / Asthma	Inhalation solution	HCQ01 (Hydroxychloroquine sulfate)	Phase I/II (NCT04731051)
Pulmonary Tuberculosis	Aerosol inhalation solution	Ad5Ag85A	Phase I (NCT02337270)
COVID-19 / Viral Infections	Nebulizer inhalation solution	Captopril	Phase II (NCT04355429)
COVID-19 / Viral Infections	Powder for inhalation solution	Recombinant t-PA	Phase II (NCT04356833)
COPD / Asthma	Excipient-free dry powder	Ivermectin	Phase III (NCT04681053)
COVID-19 / Viral Infections	Nasal spray	Sodium Pyruvate	Phase II/III (NCT04824365)
COVID-19 / Viral Infections	Inhalation solution	Ribavirin (Virazole®)	Phase I (NCT04551768)
Cystic Fibrosis	Inhalation solution	Levofloxacin (Aeroquin®, MP-376)	Phase III (NCT01270347, NCT01180634)
COPD / Asthma	Aerosol SPRAY	Ciclesonide (OMNARIS)	Phase II (NCT04381364, NCT04330586)
COVID-19 / Viral Infections	Natural nano-sized vesicles for inhalation	EXO1, EXO2	Phase II (NCT04491240, NCT04602442)
COVID-19 / Viral Infections	Inhalation solution	Aviptadil (Synthetic VIP)	Phase II (NCT04536350)
COPD / Asthma	Inhalation solution	ILOPROST (VENTAVIS)	Phase II (NCT04445246)
Cystic Fibrosis	Inhalation solution	Dornasealfa (Pulmozyme®)	Marketed
COVID-19 / Viral Infections	Inhalation solution	PUL-042	Phase II (NCT04312997, NCT04313023)
COPD / Asthma	Nanoparticle powder for inhalation	Remdesivir (VEKLURY, GS-5734™)	Phase I (NCT04480333)
COVID-19 / Viral Infections	Nebulizer inhalation solution	GM-CSF (Molgramostim)	Phase II (NCT04569877)
Cystic Fibrosis	Excipient-free spray-dried powder	Colistimethate sodium (Colobreathe®)	Marketed
COVID-19 / Viral Infections	Nasal spray	Ivermectin	Phase II (NCT04510233)
COVID-19 / Viral Infections	Nebulizer inhalation solution	Ad5-nCoV (Recombinant Coronavirus Vaccine)	Phase I (NCT04552366), I/II (NCT04840992)
COVID-19 / Viral Infections	Nano vesicles (COVID-19 T cell derived)	CSTC-Exo	Phase I (NCT04389385)
Cystic Fibrosis	Inhalation solution	Colistimethate sodium (Promixin®)	Marketed
Cystic Fibrosis	Inhalable dry powder	Ciprofloxacin (Cipro Inhale, BAYQ3939)	Phase III (NCT01764841)
COPD / Asthma	Dry powder for nebulization	Aviptadil acetate (ZYESAMI™)	Phase II/III (NCT04360096)
COVID-19 / Viral Infections	Nebulizer inhalation solution	Saline + 0.3% hyaluronic acid (Yabro®)	Phase II (NCT04830020)
COPD / Asthma	Dry powder inhaler	Budesonide (PULMICORT)	Phase II (NCT04416399)
Cystic Fibrosis	Inhalation solution	Dornasealfa (Pulmozyme®)	Marketed

Future Perspective

Despite the numerous challenges associated with pulmonary drug delivery, interest in this route continues to grow rapidly—underscoring a clear recognition of its therapeutic advantages. In recent years, there has been significant progress in treatments for asthma and COPD, particularly through improvements in inhaler design, formulation strategies, and patient adherence. These trends are expected to continue, driven by the growing need for effective and

patient-friendly respiratory therapies. Future developments are likely to focus on repurposing existing drugs for inhalation to address both common and rare respiratory diseases. Examples already in practice include inhaled interferon-gamma for idiopathic pulmonary fibrosis, cyclosporine for lung transplant rejection, rifampicin and capreomycin for tuberculosis, and voriconazole for pulmonary aspergillosis. Pharmaceutical efforts are increasingly centered on maximizing pulmonary deposition through optimized formulations and inhaler designs aimed at improving both local and systemic drug action. While current strategies mainly rely on existing delivery platforms, emerging approaches such as the incorporation of protease inhibitors, PEGylation for molecular protection, and targeting airway immunoglobulin receptors for protein transcytosis offer promising potential. There is growing interest in extending drug residence time in the lungs to enhance therapeutic effects. Controlled-release formulations enabling once-daily dosing from traditionally twice-daily drugs could significantly improve patient adherence. Among these, liposomal formulations have shown the most progress, with some advancing to late-stage clinical trials. Though various controlled-release systems—such as large porous particles containing PLGA—have been studied, their clinical translation remains limited. Inhaled nanomedicine remains an early-stage field, with recent efforts focusing on PLGA-based nanoparticles and nanoparticle-loaded liposomes. While inhalation may not be suitable for all respiratory conditions, it holds considerable promise as a complementary route to oral or parenteral delivery in select cases.

CONCLUSION

Pulmonary drug delivery systems (PDDS) have emerged as a transformative modality in both local and systemic therapy, offering rapid onset of action, enhanced drug bioavailability, and improved patient compliance. The strategic advantages of the pulmonary route—such as bypassing first-pass metabolism, large absorptive surface area, and non-invasiveness—have catalyzed the development of diverse therapeutic agents, from conventional small molecules to advanced biologics, gene therapies, and vaccines. Recent innovations in formulations—including nanoparticles, liposomes, niosomes, microspheres, nanosuspensions, and microemulsions—have significantly enhanced the efficiency, targeting, and retention of drugs within the pulmonary tract. Simultaneously, device advancements such as pMDIs, DPIs, nebulizers, and smart inhalers have improved dosing precision and patient adherence, with smart technology enabling real-time monitoring and remote care. Despite these strides, challenges remain. Anatomical and physiological barriers, formulation complexities, patient-related factors, and drug-specific physicochemical properties continue to impact delivery efficiency and therapeutic outcomes. Moreover, translating promising preclinical strategies into clinically viable therapies is often hindered by a limited pool of suitable excipients and animal models. Nonetheless, the future of PDDS is promising. With expanding applications in non-respiratory systemic diseases, gene and RNA-based treatments, and inhalable vaccines, pulmonary delivery is poised to redefine modern therapeutic strategies. Ongoing research focused on overcoming current limitations, coupled with the integration of personalized medicine and digital health, will further refine and expand the role of PDDS in both acute and chronic disease management.

REFERENCE:

1. Naghavi M, Antony C, Brauer M, Cohen A, Hay S, Krohn K, et al. Global burden of chronic respiratory diseases and risk factors, 1990–2019: an update from the Global Burden of Disease Study 2019. *eClinical Medicine*. 2023 Apr 25;63:101936. doi: 10.1016/j.eclinm.2023.101936.
2. Dhege CT, Kumar P, Choonara YE. Pulmonary drug delivery devices and nanosystems as potential treatment strategies for acute respiratory distress syndrome (ARDS). *Int J Pharm*. 2024;657:124182. doi: 10.1016/j.ijpharm.2024.124182.
3. Rathod HK, Katekar VA, Dhole YR, Nalinde PS. Pulmonary drug delivery system: A review. *GSC Biol Pharm Sci*. 2023;25(3):149–58. doi: 10.30574/gscbps.2023.25.3.0473.
4. Sen O, Sarkar P, Das S, Giri NK, Sarkar S, Jana S, et al. Membrane permeability and drug targeting potential of phospholipid-based nanocarriers in lung cancer therapy. *ChemistrySelect*. 2024;9(40). doi: 10.1002/slct.202403174.
5. Calle Rubio M, AdamiTeppa PJ, Rodríguez Hermosa JL, GarcíaCarro M, TallónMartínez JC, Riesco Rubio C, et al. Insights from real-world evidence on the use of inhalers in clinical practice. *J Clin Med*. 2025;14(4):1217. doi: 10.3390/jcm14041217.
6. Pham TQ, Delorme L, Cortaredona S, Ranque S, Menu E. Pulmonary aspergillosis: epidemiology and unresolved diagnostic challenges—insights from a two-year retrospective cohort study in Marseille. *Respir Med*. 2025;108206. doi: 10.1016/j.rmed.2025.108206.
7. Newman S. Drug delivery to the lungs: Challenges and opportunities. *TherDeliv*. 2017;8:647–61. doi: 10.4155/tde-2017-0037.
8. Jurado-Palomo J, et al. A newly developed, easy-to-use prehospital drug-derived score compared with three conventional scores: A prospective multicenter study. *Eur J Clin Invest*. 2025;55(1):e14329.
9. Banat H, Ambrus R, Csóka I. Drug combinations for inhalation: Current products and future development addressing disease control and patient compliance. *Int J Pharm*. 2023;643:123070. doi: 10.1016/j.ijpharm.2023.123070.
10. He S, Gui J, Xiong K, et al. A roadmap to pulmonary delivery strategies for the treatment of infectious lung diseases. *J Nanobiotechnol*. 2022;20:101. doi: 10.1186/s12951-022-01307-x.
11. Levin P, Hoogwerf BJ, Snell-Bergeon J, Vigers T, Pyle L, Bromberger L. Ultra rapid-acting inhaled insulin improves glucose control in patients with type 2 diabetes mellitus. *EndocrPract*. 2021;27(5):449–54. doi: 10.1016/j.eprac.2020.10.004.
12. Greene SF, Nikula KJ, Poulin D, McInally K, Reynolds JA. Long-term nonclinical pulmonary safety assessment of Afrezza, a novel insulin inhalation powder. *ToxicolPathol*. 2020;49(2):334–48. doi: 10.1177/0192623320960420.
13. Parthvi R, Mehra S. Technosphere insulin–induced pulmonary infiltrate. *Am J Ther*. 2021;28(6):e724–6. doi: 10.1097/MJT.0000000000001154.
14. Choudhury H, Pandey M, Chauhan N, Gorain B, Taneja S, Kesharwani P. Recent advances in microsphere-based inhalation therapy for treatment of pulmonary diseases. *Drug Discov Today*. 2023;28(9):103686. doi: 10.1016/j.drudis.2023.103686.
15. Weers J. Comparison of phospholipid-based particles for sustained release of ciprofloxacin following pulmonary administration to bronchiectasis patients. *PulmTher*. 2019;5:127–50. doi: 10.1007/s41030-019-00104-6.
16. Kumar Subramani P, P N R, Narayanasamy D. The role of pulmonary drug delivery in modern therapeutics: An overview. *Cureus*. 2024;16(9):e68639. doi: 10.7759/cureus.68639.
17. O'Connor L, Behar S, Tarrant S, et al. Rationale and design of Healthy at Home for COPD: An integrated remote patient monitoring and virtual pulmonary rehabilitation pilot study. *Pilot Feasibility Stud*. 2024;10:131. doi: 10.1186/s40814-024-01560-x.

18. Zhuang M, Hassan I, Ahmad WA, Abdul Kadir A, Liu X, Li F, et al. Effectiveness of digital health interventions for chronic obstructive pulmonary disease: Systematic review and meta-analysis. *J Med Internet Res*. 2025;27:e76323. doi: 10.2196/76323.

19. Gelbman BD, Reed CR. An integrated, multimodal, digital health solution for chronic obstructive pulmonary disease: Prospective observational pilot study. *JMIR Form Res*. 2022;6(3):e34758. doi: 10.2196/34758.

20. Sibiya N, Mbatha B, Ngubane P, Khathi A. Celebrating a century of insulin discovery: A critical appraisal of the emerging alternative insulin delivery systems. *Curr Drug Deliv*. 2023;20(6):656–68. doi: 10.2174/1567201819666220531101203.

21. Cooper W, Ray S, Aurora SK, Shrewsbury SB, Fuller C, Davies G, et al. Delivery of dihydroergotaminemesylate to the upper nasal space for the acute treatment of migraine: Technology in action. *J Aerosol Med Pulm Drug Deliv*. 2022;35(6):321–32. doi: 10.1089/jamp.2022.0005.

22. Agnihotri V, Agrawal Y, Goyal S, Sharma C, Ojha S. An update on advancements and challenges in inhalational drug delivery for pulmonary arterial hypertension. *Molecules*. 2022;27(11):3490. doi: 10.3390/molecules27113490.

23. Yang L, Zhang L, Luo Z. Comparative pharmacokinetics and bioequivalence evaluation of two formulations of pramipexoledi hydro chloride extended-release tablets in healthy Chinese subjects under fasted and fed states: A randomized, open-label, single-dose, two-period crossover clinical trial. *Drug Des DevelTher*. 2023;17:2369–81. doi: 10.2147/DDDT.S421449.

24. Liu F, Xin M, Feng H, Zhang W, Liao Z, Sheng T, et al. Cryo-shocked tumor cells deliver CRISPR-Cas9 for lung cancer regression by synthetic lethality. *Sci Adv*. 2024;10(13):eadk8264.doi: 10.1126/sciadv.adk8264. Epub 2024 Mar 29. PMID: 38552011; PMCID: PMC10980270.

25. Zhang YB, Xu D, Bai L, Zhou YM, Zhang H, Cui YL. A review of non-invasive drug delivery through respiratory routes. *Pharmaceutics*. 2022;14(9):1974. doi: 10.3390/pharmaceutics14091974.

26. Wei T, Sun Y, Cheng Q, Chatterjee S, Traylor Z, Johnson LT, et al. Lung SORT LNPs enable precise homology-directed repair mediated CRISPR/Cas genome correction in cystic fibrosis models. *Nat Commun*. 2023;14(1):7322. doi: 10.1038/s41467-023-42948-2.

27. Huayamares SG, Zenhausern R, Loughrey D. Nanocarriers for inhaled delivery of RNA therapeutics. *Curr Res Biotechnol*. 2024;7:100200. doi: 10.1016/j.crbiot.2024.100200.

28. Wang Y, Fu M, Liu J, Yang Y, Yu Y, Li J, et al. Inhibition of tumor metastasis by targeted daunorubicin and dioscincodelivery liposomes modified with PFV for the treatment of non-small-cell lung cancer. *Int J Nanomedicine*. 2019;14:4071–90. doi: 10.2147/IJN.S194304.

29. Hussen BM, Najmadden ZB, Abdullah SR, et al. CRISPR/Cas9 gene editing: a novel strategy for fighting drug resistance in respiratory disorders. *Cell Commun Signal*. 2024;22:329. doi: 10.1186/s12964-024-01713-8.

30. Huang C, Li H, Duan X, Zhang P, Qi S, Du J, et al. Inhaled non-viral delivery systems for RNA therapeutics. *Acta Pharm Sin B*. 2025;15(5):2402–30. doi: 10.1016/j.apsb.2025.03.033.

31. Heida R, Frijlink HW, Hinrichs WLJ. Inhalation of vaccines and antiviral drugs to fight respiratory virus infections: reasons to prioritize the pulmonary route of administration. *mBio*. 2023;14:e01295-23. doi: 10.1128/mbio.01295-23.

32. Klein TO, Soll BA, Issel BF, Fraser C. Bronchus-associated lymphoid tissue lymphoma and Mycobacterium tuberculosis infection: An unusual case and a review of the literature. *Respir Care*. 2007;52(6):755–8.

33. Counoupas C, Ferrell KC, Ashhurst A, et al. Mucosal delivery of a multistage subunit vaccine promotes development of lung-resident memory T cells and affords interleukin-17-dependent protection against pulmonary tuberculosis. *NPJ Vaccines*. 2020;5:105. doi: 10.1038/s41541-020-00255-7.

34. Zhou M, Xiao H, Yang X, Cheng T, Yuan L, Xia N. Novel vaccine strategies to induce respiratory mucosal immunity: advances and implications. *MedComm (2020)*. 2025;6(2):e70056. doi: 10.1002/mco2.70056.

35. Overton ET, Goepfert PA, Cunningham P, Carter WA, Horvath J, Young D, et al. Intranasal seasonal influenza vaccine and a TLR-3 agonist, rintatolimod, induced cross-reactive IgA antibody formation against avian H5N1 and H7N9 influenza HA in humans. *Vaccine*. 2014;32(42):5490–5. doi: 10.1016/j.vaccine.2014.07.078.

36. Tero-Losada M, Petrovsky N, Alami A, Crispo JA, Mattison D, Capani F, et al. Disproportionality analysis of adverse neurological and psychiatric reactions with the ChAdOx1 (Oxford-AstraZeneca) and BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines in the United Kingdom. *Expert Opin Drug Saf*. 2022;22(4):343–9. doi: 10.1080/14740338.2022.2120607.

37. Chen J, Wang P, Yuan L, Zhang L, Zhang L, Zhao H, et al. A live attenuated virus-based intranasal COVID-19 vaccine provides rapid, prolonged, and broad protection against SARS-CoV-2. *Sci Bull*. 2022;67(13):1372–87. doi: 10.1016/j.scib.2022.05.018.

38. Setiabudiawan TP, Reurink RK, Hill PC, Netea MG, van Crevel R, Koeken VACM. Protection against tuberculosis by Bacillus CalmetteGuérin (BCG) vaccination: a historical perspective. *Med (Cell Press)*. 2022;3(1):6–24. doi: 10.1016/j.medj.2021.11.006.

39. Yan R, Zou C, Yang X, Zhuang W, Huang Y, Zheng X, et al. Nebulized inhalation drug delivery: clinical applications and advancements in research. *J Mater Chem B*. 2025;13(3):821–43. doi: 10.1039/D4TB01938E.

40. Hagmeyer L, van Koningsbruggen-Rietschel S, Matthes S, Rietschel E, Randerath W. From the infant to the geriatric patient—strategies for inhalation therapy in asthma and chronic obstructive pulmonary disease. *ClinRespir J*. 2023;17(6):487–98. doi: 10.1111/crj.13610.

41. Burgess SW, Sly PD, Cooper DM, Devadason SG. Novel spacer device does not improve adherence in childhood asthma. *PediatrPulmonol*. 2007;42(8):736–9. doi: 10.1002/ppul.20647.

42. Schreiber J, Sonnenburg T, Luecke E. Inhaler devices in asthma and COPD patients – a prospective cross-sectional study on inhaler preferences and error rates. *BMC Pulm Med*. 2020;20:222. doi: 10.1186/s12890-020-01246-z.

43. Hodder R, Price D. Patient preferences for inhaler devices in chronic obstructive pulmonary disease: experience with Respimat Soft Mist inhaler. *Int J Chron Obstruct Pulmon Dis*. 2009;4:381–90. doi: 10.2147/copd.s3391.

44. Al-Tabakha MM. Future prospect of insulin inhalation for diabetic patients: The case of Afrezza versus Exubera. *J Control Release*. 2015;215:25–38. doi: 10.1016/j.jconrel.2015.07.025.

45. Chawhan A, Thakrar D, Pinto L. Inhaler devices and their challenges - Helping patients use inhalers. *Lung India*. 2023;40:303–5. doi: 10.4103/lungindia.lungindia_24_23.

46. Sosnowski TR. Towards more precise targeting of inhaled aerosols to different areas of the respiratory system. *Pharmaceutics*. 2024;16(1):97. doi: 10.3390/pharmaceutics16010097.

47. Farkas A, Balásházy I. Quantification of particle deposition in asymmetrical tracheobronchial model geometry. *ComputBiol Med*. 2008;38(4):508–18. doi: 10.1016/j.compbiomed.2008.01.014.

48. Zhou G, Liu Z, Shao W, Sun B, Li L, Liu J, et al. Study on the effects of dust particle size and respiratory intensity on the pattern of respiratory particle deposition in humans. *Indoor Air*. 2024. doi: 10.1155/2024/5025616.

49. Shen AM, Minko T. Pharmacokinetics of inhaled nanotherapeutics for pulmonary delivery. *J Control Release*. 2020;326:222–44. doi: 10.1016/j.jconrel.2020.07.011.

50. Boboltz A, Kumar S, Duncan GA. Inhaled drug delivery for the targeted treatment of asthma. *Adv Drug Deliv Rev*. 2023;198:114858. doi: 10.1016/j.addr.2023.114858.

51. Chang RYK, Chan HK. Advancements in particle engineering for inhalation delivery of small molecules and biotherapeutics. *Pharm Res*. 2022;39(12):3047–61. doi: 10.1007/s11095-022-03363-2.

52. Chang RYK, Chan HK. Advancements in particle engineering for inhalation delivery of small molecules and biotherapeutics. *Pharm Res*. 2022;39(12):3047–61. doi: 10.1007/s11095-022-03363-2.

53. Thevarkattil AM, Yousaf S, Houacine C, Khan W, Bnyan R, Elhissi A, et al. Anticancer drug delivery: Investigating the impacts of viscosity on lipid-based formulations for pulmonary targeting. *Int J Pharm*. 2024;664:124591. doi: 10.1016/j.ijpharm.2024.124591.

54. Çakmaklı S, Özdemir A, Fırat H, Aypak C. An evaluation of the use of inhalers in asthma and chronic obstructive pulmonary disease. *J TaibahUniv Med Sci*. 2023;18(4):860–7.