Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Inhalation: A Smart Strategy and Increasing Potential for Drug Delivery

Shao-Cheng Wang[1,2,*], Tsu-Hsiang Kuo[3,*], Chung-I Rai[4], Yuan-Chuan Chen[5,6]

[1]Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, 833, Taiwan; [2]Department of Psychiatry, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, 801, Taiwan; [3]Department of Rehabilitation Science, Jenteh Junior College of Medicine, Nursing and Management, Hou-Loung Town, Miaoli County, 356006, Taiwan; [4]Department of Cosmetic Science, Vanung University, Chung-Li City, Taoyuan, 320676, Taiwan; [5]Department of Nursing, Jenteh Junior College of Medicine, Nursing and Management, Hou-Loung Town, Miaoli County, 356006, Taiwan; [6]Department of Medical Technology, Jenteh Junior College of Medicine, Nursing and Management, Hou-Loung Town, Miaoli County, 356006, Taiwan

*These authors contributed equally to this work

Correspondence: Yuan-Chuan Chen, Email yuchuan1022@gmail.com

Abstract: The delivery of inhaled drugs is a critical and evolving strategy in modern medicine that offers distinct advantages over other routes of administration. Compared to traditional methods such as oral, intravenous, or transdermal delivery, inhalation provides rapid onset, high local drug concentrations, reduced systemic side-effects, and improved patient compliance. In addition to its established use for the treatment of respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), recent technological advancements have expanded its application in systemic therapies, vaccines, and biologics. Innovative devices like dry powder inhalers, soft mist inhalers, and smart inhalers, integrated with digital health technologies, enable precise dosing, adherence monitoring, and potential personalization of therapy. Emerging trends, such as inhaled nanoparticles, gene and RNA therapies, and inhaled vaccines, have redefined the landscape of inhalation drug delivery. Despite these advances, challenges remain in terms of formulation stability, device compatibility, interpatient variability, and environmental concerns related to propellants. Future research should emphasize green technologies, integration with telehealth, patient-specific inhaler matching, and broader therapeutic applications beyond pulmonary diseases. As device engineering, digital health, and biopharmaceutical research converge, inhalation therapy has become an essential component of precision and patient-centric medicine, providing new avenues for disease treatment and prevention under both local and systemic conditions.

Keywords: drug delivery, administration route, inhalation device, inhaled drug

Routes of Drug Administration

Drug delivery is critical for disease therapy and prevention because it is closely associated with drug safety and effectiveness. Therefore, a correct and precise choice of drug delivery is required for patients. Currently, the major drug delivery systems include topical cream/emulsion/ointment/gel, transdermal patches, oral administration, intravenous (IV) injection, intramuscular (IM) injection, subcutaneous (SC) injection, microneedles, and inhalation. A comparison of the various drug delivery systems is presented in Table 1 and Figures 1 and 2.

The choice of drug administration route is complex and dependent on drug characteristics, patient traits, and disease types, as follows:[17–20] (1) Drug nature: Chemical properties (eg, easily broken down by stomach acid or digestive enzymes), fat-soluble or water-soluble, molecular size and structure, and sensitivity to heat, light, or oxygen. (2) Drug action: Sites of action (eg, systemic like blood pressure medication or topically like eye drops or skin ointments), required release rate (eg, rapid onset of action like a pain reliever or long-acting sustained release like a chronic disease), and accessibility of target cells or organs (eg, some areas like the blood–brain barrier require special designs for penetration). (3) Patient compliance: Age and physical condition (eg, infants or the elderly are not suitable for injections or swallowing large pills), acceptability (eg, some patients do not like injections and prefer oral or inhaled medications), and convenience (eg, complex dosage forms may reduce patients' willingness to continue taking medication when

https://doi.org/10.2147/DDDT.S575392
Received: 19 October 2025
Accepted: 29 January 2026
Published: 12 February 2026

Table 1 Comparison of Major Delivery Systems

Delivery	**Topical Cream**	**Transdermal Patch**	**Oral**	**Intravenous**	**Intramuscular**	**Subcutaneous**	**Microneedle**	**Inhalation**
Description	A cream to be smeared on the skin	An adhesive patch to be placed on the skin	Uptake of drugs by swallowing or drinking through mouth	An injection into a vein and directly into the bloodstream	An injection deep into the muscle to allow the bloodstream to absorb quickly	An injection given just on the subcutaneous tissues of skins	Micro-size needles are aligned on the surface of a small patch	Uptake of drugs by inhaler through mouths or noses
Mechanism of delivery	Drugs permeate through skin pores	Drugs permeate stratum corneum barrier and diffuse across the skin	Drugs enter the body through digestive tracts and spread through the blood stream	Drugs are placed directly in the vein and spread through the blood stream	Drugs placed directly in the muscle and spread through the blood stream	Drugs are placed directly in the dermis and spread through the blood stream	Drugs bypass stratum corneum and are placed directly in the epidermis or dermis	Drugs enter the body through respiratory tracts and spread through the blood stream
Action	Local	Local	Systemic	Systemic	Systemic	Systemic	Systemic	Local or systemic
Onset	Slow	Slow	Slow	Fast	Fast	Fast	Fast	Fast
Pain	No	No	No	Yes	Yes	Yes	No	No
Bioavailability	Poor	Insufficient	Insufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
Self-administration	Yes	Yes	Yes	No	Possible	No	Yes	Yes
Reference	[1, 2]	[3, 4]	[5, 6]	[7, 8]	[9, 10]	[11, 12]	[13, 14]	[15, 16]

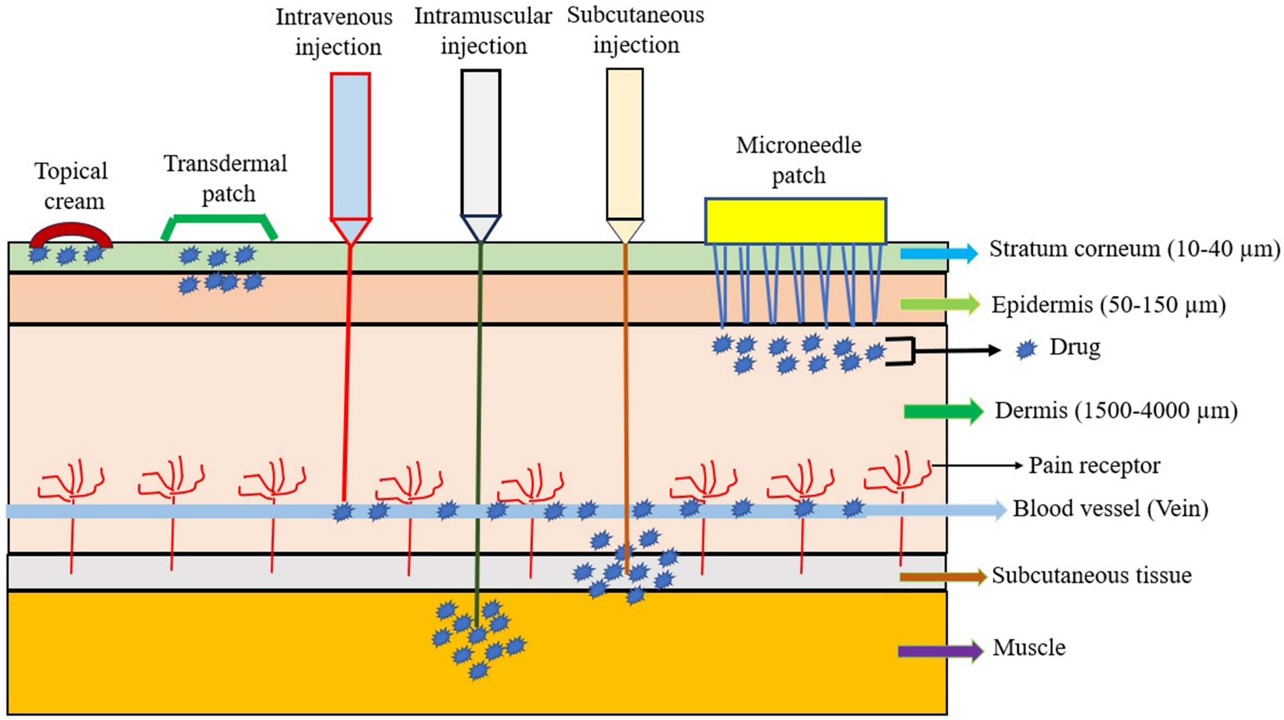

Figure 1 Comparison of drugs delivered by topical cream, transdermal patch, intravenous injection, intramuscular injection, subcutaneous injection, and microneedles.

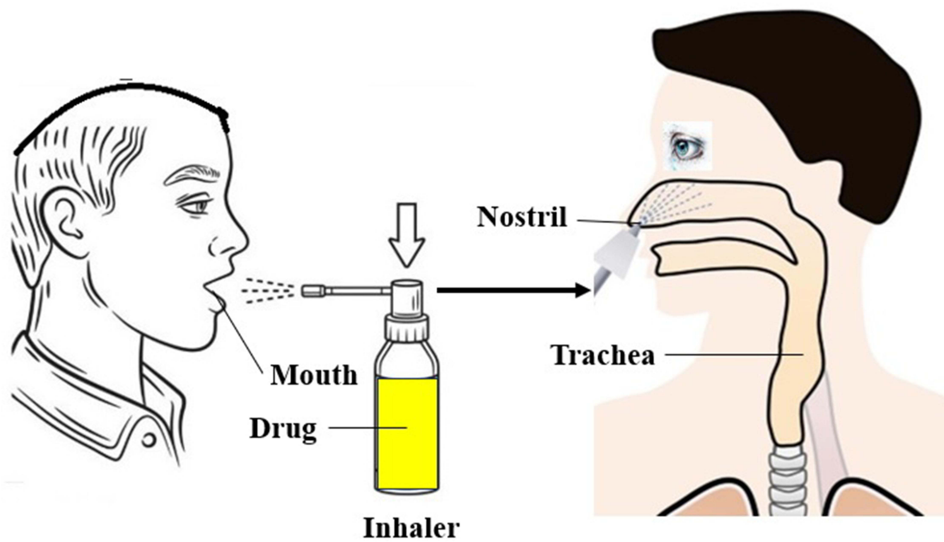

Figure 2 Different from oral administration, where drugs are taken into the digestive system by swallowing or drinking, inhalation administration means that drugs are delivered to the respiratory system through nostrils or mouths using inhalers.

providing home care). (4) Pharmacokinetics: Absorption (eg, some drugs are poorly absorbed orally and need to be administered by injection or other routes), distribution (eg, drugs will be effectively distributed to the site of action), metabolism (eg, oral administration may have a strong first-pass effect to reduce the effective concentration), and elimination (eg, some drugs may be easily and rapidly degraded in the liver and eliminated in the kidneys).

 https://doi.org/10.2147/DDDT.S575392

Why Inhalation Drugs are Important

Inhalation drugs offer several unique advantages for treating specific medical conditions, especially those related to the lungs and the respiratory system. Drugs commonly administered via inhalation include bronchodilators (eg, salbutamol and formoterol), corticosteroids (eg, fluticasone and budesonide), antibiotics (eg, tobramycin for cystic fibrosis), insulin (eg, Technosphere insulin-Afrezza ®), and pain medications (under research for systemic delivery). The following are the main reasons and examples to show that drug inhalation is important.

Direct Delivery to the Lungs

The rapid onset of action of inhaled medications is primarily attributable to the unique anatomy and physiology of the lungs. The human lungs contain an extensive network of branching airways that terminate in millions of alveoli, providing a large surface area for gas and drug exchange. The alveolar epithelium is extremely thin and lies in close proximity to a dense pulmonary capillary network, enabling rapid diffusion of inhaled drugs into the bloodstream. In addition, the lungs receive the entire cardiac output, ensuring efficient systemic absorption. These anatomical and physiological features allow inhaled drugs to reach their target site—the bronchial tree and alveoli—quickly, making this route particularly effective in emergency situations such as acute asthma attacks.

Asthma is a common chronic inflammatory disease of the airways and remains a major cause of morbidity and mortality among children and young people. The disease is characterized by airway inflammation, bronchial hyperresponsiveness, smooth muscle constriction, mucosal edema, and increased mucus production, all of which narrow the airways and increase airflow resistance. Following an asthma attack, there is an important opportunity to prevent future exacerbations by evaluating treatment adherence and optimizing long-term asthma control.[21] Careful identification of asthma triggers, anatomical and functional factors contributing to airway obstruction, barriers related to health beliefs, and socioeconomic influences is essential, as these factors may have contributed to the exacerbation.[21] Most children with asthma experience significant symptom relief with low-dose inhaled corticosteroids, which act locally on the airway mucosa to reduce inflammation while minimizing systemic exposure.[21] Although symptoms may not always appear severe at presentation, patients with acute asthma attacks frequently require emergency department management due to significant impairment of respiratory function. Early functional assessment should focus on vital signs, respiratory rate, oxygen saturation, and the degree of perceived dyspnea.[22] From a physiological perspective, airflow limitation during an asthma attack can lead to air trapping and dynamic pulmonary hyperinflation, which increase the work of breathing and compromise ventilatory mechanics. When these changes progress, immediate intervention is required. Prompt delivery of inhaled bronchodilators directly to the airways and, when necessary, intravenous therapy should be initiated to treat refractory symptoms and prevent further deterioration of respiratory function.[22]

Effective for Respiratory Diseases

Inhalation is ideal for respiratory conditions, because it delivers the drug directly to the site of action. Therefore, inhalation is the first-line delivery method for many respiratory diseases related to the lungs, such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and pulmonary infections, including coronavirus infectious disease 2019 (COVID-19).

The worse outcomes of COPD may result from decreased adherence and increase the risk of disease exacerbation, and long-term mortality. Factors that may influence adherence are related to patients, clinicians, and the healthcare system.[23] Among the clinician factors, it is crucial to deliver simplified treatment regimens using an inhaler adapted to the patient.[23] Smart inhalers and simplified treatment regimens can effectively improve adherence and long-term outcomes in COPD.[23]

Lung infection by bacteria such as *Pseudomonas aeruginosa* is the most important cause of death in cystic fibrosis; therefore, antimicrobial therapy is a major strategy for the management of microbial infections.[24] The major and effective control approaches for patients with cystic fibrosis include rigorous microbiological surveillance, intensive eradication therapy, and long-term maintenance therapy based on inhaled antibiotics.[24]

The development of COVID-19 treatment is still needed to improve outcomes, although global approval and distribution of vaccination programs have significantly prevented infection with the severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2). In the early pandemic period, patients with pre-existing asthma or COPD were under-represented among those with COVID-19.[25] Inhaled corticosteroids routinely taken by patients with asthma and COPD could effectively protect against severe COVID-19 in clinical studies, indicating that it may be a potential treatment for COVID-19.[25]

Lower Dosage Requirements

Because of the targeted delivery, the required inhalation drug dose is usually lower than that of other traditional routes, such as oral administration or injection. They are transmitted directly to the lungs to have a higher local concentration so that the treatment is effective at lower doses compared to systemic administration, thus minimizing drug waste.

Local pulmonary delivery of biopharmaceuticals may provide some advantages for the treatment of lung diseases, such as the rapid onset of action, reduced systemic exposure, needleless administration, and particularly lower dose requirements.[26] However, it is challenging to formulate a protein for inhaled delivery and requires proteins with favorable biophysical properties to adapt to the forces related to the formulation, delivery, and inhalation devices.[26] Nanobodies derived from naturally occurring heavy-chain-only immunoglobulins are highly soluble, stable, and exhibit biophysical characteristics suitable for pulmonary delivery well.[26] Nanobodies have been shown to be delivered via the pulmonary route, and it is advantageous to use them for inhaled delivery to the lung; for example, a nanobody (ALX-0171) could be used for the effective treatment of respiratory syncytial virus (RSV) infections at very low doses in clinical development.[26]

Reduced Systemic Side-Effects

Inhalation drugs usually act on target organs, minimizing drug exposure to the rest of the body and thus reducing systemic side-effects. Their systemic side-effects are lower because fewer drugs circulate in the bloodstream than via oral or injectable routes.

Systemic administration of cytotoxic chemotherapy for cancer therapy administered intravenously and orally is known to cause severe and debilitating systemic side-effects. Regional therapy with cytotoxic agents potentially reduces the extent of drug exposure and risk of systemic side-effects.[27] Inhaled cytotoxic chemotherapy can be used as an effective regional therapy for both primary lung cancer and lung metastases from other primary tumors to avoid the side-effects of systemic therapy.[27] Moreover, some aerosol chemotherapeutic agents are absorbed directly into arterial circulation, showing therapeutic effects at extrapulmonary sites.[27] Currently, aerosol administration of several different chemotherapeutic agents is still being evaluated either in preclinical settings or in early phase human trials.[27] Some studies have indicated that inhaled chemotherapy is feasible and effective for treating lung tumors with reduced systemic side-effects.[27]

Non-Invasive and Convenient

Inhalation drugs via oral, pulmonary, and nasal delivery using inhalers and nebulizers are easy to use at home. It is suitable for the long-term treatment of patients with chronic diseases for convenience and to avoid the discomfort caused by injections.

The potency and specificity of biologics make them more important drugs than conventional chemical drugs for the treatment of certain diseases. However, it is difficult to administer biologics noninvasively because of their intrinsic characteristics such as high molecular weight, hydrophilicity, and instability.[28] In particular, long-term administration is required when biologics are used to treat chronic disorders. Consequently, researches made many efforts to develop a formulation for non-invasive administration routes for the improvement of patient compliance and convenience for use at home.[28] Strategies for non-invasive delivery, including oral, pulmonary, and nasal delivery, have recently been discussed and evaluated.[28] Insulin, calcitonin, and heparin are the three main targets of discussion because they represent proteins, polypeptides, and polysaccharide drugs, respectively.[28]

Potential for Systemic Delivery

Some inhalation drugs are designed for systemic effects based on the large surface area of the lungs and the blood supply, such as inhalable insulins (eg, Afrezza), pain medications, vaccines, lung cancer therapeutics, and drugs for gene therapy.

The administration of repurposed non-oncology drugs loaded in nanocarriers through inhalation may act as an alternative strategy for the treatment of lung cancer, owing to the insufficiency of first-line chemotherapeutics, the presence of resistant tumors, and inappropriate routes of administration.[29] Site-specific release using a suitable inhalation device may provide enhanced efficacy, reduce mortality, and improve the quality of life of patients.[29]

Mouse cytomegalovirus (MCMV) has been used as an intranasal and injectable gene therapy system to successfully extend the lifespan of animals.[30] Glucose tolerance and physical performance were specifically improved, with no loss of body mass or alopecia.[30] Intranasal and injectable preparations would deliver gene therapy to multiple organs safely and efficiently, having long-term persistence advantages, and without carcinogenicity or side-effects.[30]

Type of Inhalation

Inhalation drug delivery systems are categorized based on the device used and form of the drug (gas, mist, powder, etc). Inhalation is generally classified into the following categories: nasal inhalation (through the nose), oral/pulmonary inhalation (through the mouth into the lungs), steam inhalation (through the nose and/or mouth), and volatile anesthetic inhalation (through an anesthetic mask). Among these, nasal and oral inhalation are the main routes of drug administration.

Nasal inhalation is a method of administering medications directly into the respiratory tract, including the lungs, through the nostrils. This novel approach is used for the treatment of both local and systemic of diseases, particularly those affecting the lungs like asthma, COPD, and cystic fibrosis. Additionally, nasal inhalation vaccines have been used to prevent diseases caused by respiratory pathogens such as SARS-CoV-2,[31,32] influenza virus,[33] RSV,[34] and *Mycobacterium tuberculosis*.[35] Inhalation has been extensively used for drug delivery and has increasing potential for the therapy and prevention of diseases (Table 2).

Table 2 Comparison of Nasal Inhalation and Oral Inhalation

Aspect	Nasal Inhalation	Oral Inhalation
Entry route	Nostril	Mouth
Primary target site	Nasal mucosa	Lungs (alveoli, bronchi)
Onset of action	Fast, especially for local or CNS effects	Fast, especially for bronchodilators and systemic drugs
Absorption site	Nasal epithelium, olfactory region	Alveolar-capillary membrane
Systemic delivery	Possible (eg, desmopressin, naloxone)	Common for asthma, COPD drugs, insulin, etc.
Local delivery use	Allergic rhinitis, nasal congestion	Asthma, COPD, cystic fibrosis
Bypasses first-pass metabolism	Yes	No
Drug form example	Spray, drop, gel	pMDI, DPI, nebulizer
Device	Nasal spray/delivery pump	Inhalers (MDI, DPI), nebulizer
Volume administered	Small (25–200 µL per nostril)	Variable (depend on formulations and devices)
Patient coordination required	Low	Moderate to High (especially with MDI)
Bioavailability variability	Moderate, depends on mucociliary clearance, congestion	High, depends on inhalation technique, lung deposition
Irritation potential	Possible (eg, nasal dryness, stinging)	Possible (eg, throat irritation, cough)
CNS drug access	Potential for nose-to-brain delivery	Limited (unless be systemically absorbed)
Limitations	Nasal pathology, congestion affects delivery	Requires proper technique; less effective in acute distress
Drug examples	Oxymetazoline, naloxone, desmopressin, COVID-19 vaccine (iNCOVACC®)[36]	Salbutamol, fluticasone, tiotropium, insulin, COVID-19 vaccine (Convidecia Air®)[36]
References	[37–41]	[42–46]

Abbreviations: CNS, central nervous system; COPD, chronic obstructive pulmonary disease; pMDI, pressurized metered dose inhaler; DPI, dry powder inhaler.

Oral inhalation is a drug delivery system consisting of a device and a corresponding formulation, in which drugs are taken through the mouth as a fine mist given by an inhaler. Large droplets would only prime the mouth and throat, but small droplets may be transmitted further throughout the body. The drug formulation must be designed to be consistent with the device because they must work together to achieve the intended drug effects in patients.[47] Oral inhalation drugs are usually classified into three types: pressurized metered-dose inhalers (pMDIs or MDIs), dry powder inhalers (DPIs), and nebulizers. Oral inhalation provides the possibility of targeting drugs locally to different areas of the respiratory tract or delivering them systemically using the larger surface areas of the alveoli, such as in systemic conditions (eg, diabetes and pain management) in some special therapies. Pulmozymes and inhaled insulins (eg, Exubera and Afrezza) are examples of successful pulmonary drug delivery for commercial use.[45] Although the subsequent over-reactions (eg, unproven fear of lung cancer) of Exubera may hinder the development of systemically inhalable protein and peptide drugs, many inhalable biopharmaceuticals have recently advanced to clinical trials.[45] Oral inhalable products have become possible alternatives for the delivery of small molecules, avoiding oral pharmacokinetics and/or liver first-pass effects.[45] The development of novel inhalation devices and more studies on lung physiology will promote the oral inhalation of drugs to be an attractive therapeutic strategy (Table 2).

Devices Used for Inhalation

The devices utilized for the administration of inhaled drugs are very crucial in the management of obstructive lung diseases, such as asthma and COPD. They should deliver a high proportion of fine particles, be easy to use, and offer consistent and accurate doses of the active substance to make sure a high bronchial deposition of inhaled drugs. Currently, four types of inhalers are extensively used including nebulizers, dry powder inhalers (DPIs), pressurized metered-dose inhalers (pMDIs), and soft mist inhalers (SMIs) (Table 3).

Nebulizers are used by patients who cannot use other inhalers; however, they require a long administration time and are unable to ensure precise dosages. The two most common types are jet nebulizers and vibrating-mesh nebulizers. Vibrating-mesh nebulizers perform well; however, jet nebulizers are the most commonly used. Nebulizer type should be decided after seriously considering the needs of the drug combination, diseases, patient types, target sites for deposition, healthcare professionals, and patient safety.[48] Although we may focus on other delivery devices, such as pMDIs and DPIs, nebulizers are still considered a viable and common approach for respiratory drug delivery because of the easy formulation of many drugs in water and their delivery as aqueous aerosols.[49] For example, in COPD treatment, pMDIs, DPIs, and SMIs may be appropriate for most patients with COPD; however, these devices may not be suitable for these devices.[50] Fortunately, nebulizers can provide these patients with an alternative administration route to avoid the requirement of inspiratory flow, manual dexterity, or complicate harmonization between hands and breath.[50]

DPIs are micronized drug particles attached to larger lactose carrier particles. Different DPI formulations have been developed to overcome the challenges of aerosolizing fine cohesive drug-containing particles for the development of consistent and effective DPI products.[51] Particle engineering processes can produce micron-sized drug-containing particles and their subsequent assembly into carrier-based or carrier-free components.[51] Although patients should produce an adequate inspiratory flow to extract drugs and disaggregate drugs from the carriers, it is not required to have harmonization between actuation and inhalation. Recent advances in DPIs include nanoparticle systems, siRNA-

Table 3 Types of Inhalation Devices

Device	Characteristic
Nebulizer:	Convert liquid medications into mist, useful for infants, elderly, or those with difficulty
Dry Powder Inhaler (DPI)	Breath-activated devices delivering powdered medication
Pressurized Metered-Dose Inhaler (pMDI)	Pressurized canisters delivering a specific dose per puff
Soft Mist Inhalers (SMI)	Deliver a slow-moving mist to improve lung deposition

based medications, liposomes, and delivery systems based on proliposomes.[52] For example, silver nanoparticle-based DPIs have revealed significant outcomes in the infected lungs of COVID-19 patients.[53]

pMDIs have been used as first-line treatment for pulmonary conditions since the 1950s. The development of therapies based on pMDIs will continue because of the expanding applications of pMDIs beyond asthma and COPD.[54] The pMDIs have become popular because they are small, cheap, rapid, and quiet. Their performance is improved by spacers and their delivery speed is reduced by new technologies.[55] Factors such as formulation variables on metrics controlling the performance of pMDIs can potentially benefit patients by providing improved drugs for current indications to initiate new areas of therapy.[55]

SMIs are medications dissolved in an aqueous solution without propellants and are dispensed as slow aerosol clouds resulting from the energy of a spring.[56] They can be used as reusable devices to reduce the environmental impact of inhalers and are more convenient for patients because they are propellant-free.[57] By the power of SMIs, single or multiple doses of inhalable drug aerosols in the form of slow mist are delivered to patients.[58] SMIs provide a longer and slower release of aerosols with a smaller ballistic effect than traditional inhalers, resulting in a limited loss in the oropharyngeal area.[58] Therefore, patients do not require much coordination between actuation and inhalation. Smart inhalers connected to smartphones are promising for supplementing information associated with patient adherence and inhaler techniques.[58]

Currently, innovative inhalation devices are used clinically, and their benefits are summarized in Table 4.

Emerging Trends

The delivery of inhalation drugs has long been central to the treatment of respiratory diseases such as asthma and COPD. However, recent innovations have expanded their use beyond pulmonary disorders, opening doors to systemic therapies and precision medicine. Current applications include the treatment of respiratory diseases (eg, asthma, COPD, and cystic fibrosis), systemic diseases (eg, diabetes and pain management), pulmonary infections (eg, inhaled antibiotics for *Pseudomonas aeruginosa* and tuberculosis), and disease prevention (eg, COVID-19 vaccine). The emerging trends in the development and application of inhalational drugs based on various strategies are discussed below.

Smart Inhaler Technology

A smart inhaler integrates connectivity with a mobile phone application via Bluetooth. It is built using sensor technology that can record the time and location for each use. The first smart inhaler approved by the US Food and Drug Administration (FDA) was Teva's ProAir Digihaler (albuterol sulfate), with a use-tracking real-time sensor synchronized with a mobile app.[64] These sensors may be an integral part of the inhaler or an external device attached to the primary inhaler. This device could be used to establish an automatic reminder for the next dose. Smart inhalers can help doctors and patients track conditions and monitor the efficacy of treatment over time, without the need to keep diaries or written records. By setting related notifications, smart inhaler technology is a useful tool for optimizing treatment schedules, dosage reminders, and tracking usage., This will allow both patients and doctors to know how, why, where, and when the symptoms improve or worsen (Table 5). Below are examples of asthma treatment using smart inhalers.

A smart inhaler via Bluetooth has the potential to improve patient adherence to asthma therapies and maintain their condition under control. The devices need to be designed with health systems and patients in mind so that they can provide the maximum benefit.[65]

Table 4 Technological Innovations for Inhalation Devices

Device	Benefit	Example
Dry Powder Inhaler (DPI)	Breath-actuated, no propellant requirement	Ellipta®[59,60]
Pressurized Metered-Dose Inhaler (pMDI) with Smart Dose Counters	Prevention of under-/over-dosing	Digihaler[61,62]
Soft Mist Inhalers (SMI)	Lower inspiratory effort	Respimat®[56,63]

Table 5 Summary of Innovative Strategies for the Development of Inhalation Drugs

Innovative Strategy	**Tendency**
Smart inhaler technology	• Digital inhalers with sensors for dose tracking and adherence monitoring • Devices with sensors for tracking usage and ensuring adherence • Bluetooth-enabled devices to synchronously with Apps for remote patient management • Artificial intelligence (AI) integration for predictive maintenance of inhalation therapy in chronic diseases
Inhaled biologics	• Inhaled biologics are biologic drugs delivered directly to the lungs via an inhaler, providing advantages such as rapid absorption due to the lung's large surface area • Peptides, proteins, and antibodies are being reformulated for pulmonary delivery
Nanoparticles and liposomal formulations	• Improvement of drug stability and absorption • Nanocarriers allow for sustained release and targeting of specific lung tissues
Gene, RNA and target therapies	• Pulmonary delivery of siRNA, mRNA, and CRISPR-Cas components • Target lung diseases under exploration like cystic fibrosis, lung cancer, pulmonary hypertension and COVID-19
Inhaled vaccines	• Needle-free, mucosal immunity-inducing formulations • Induction of triple immunity, including humoral, cellular, and mucosal immunity • Interception of pathogens at the first line when they invade • Dosage sparing effect • COVID-19 expedite research into inhaled mRNA and adenovirus-based vaccines
Personalized inhalation therapy	• Drugs and their inhalers must be specifically designed to suit specific patient's needs • Pharmacogenomics and AI algorithms help customize treatment regimens. • Patient-specific inhaler-device should be matched based on inspiratory flow profile

Smart spacers can monitor inhaler techniques to enhance adherence to inhaled medications and achieve better outcomes. A definitive randomized controlled trial revealed that it was feasible for smart spacer-driven education in patients with asthma to reduce inhaler errors in a short-term study.[66] However, it is necessary to assess the clinical effects in long-term and larger studies.[66]

Inhaled Biologics

Inhaled biologics (eg, peptides, proteins, enzyme and genes) are being reformulated for the pulmonary delivery of drugs delivered directly to the lungs via an inhaler to avoid gastrointestinal degradation and provide targeted delivery. The advantages of this non-invasive route include improved patient compliance, rapid onset of action, and direct access, preferably for therapy and prevention of respiratory diseases. Inhaled biologics provide benefits such as rapid absorption owing to the large surface area of the lungs (Table 5). Below are examples of treatments for COVID-19 and lung cancer using inhaled biologics.

The efficacy of first-generation COVID-19 vaccines is decreasing, and frequent breakthrough infections have facilitated the transmission and evolution of SARS-CoV-2. Some immunocompromised patients cannot be protected by COVID-19 vaccines and are still vulnerable to severe disease, although they have received three primary-dose vaccines and heterologous boosters. The evolution of new SARS-CoV-2 variants has also weakened the therapeutic efficacy of monoclonal antibodies.[67] Fortunately, inhalation treatment with angiotensin-converting enzyme 2 (ACE2) receptor has decreased the severity of COVID-19 in animal models,[68] and budesonide inhalation may be effective in randomized controlled trials.[69]

Aerosolized IgG accumulated in the lungs and tumor and aerosolized cetuximab also restricted mouse tumor growth. Although the administration of anticancer mAbs via the airways deserves further evaluation for the clinical treatment of lung cancer, it is potentially effective and may limit systemic side-effects.[70] An immunotherapeutic chitosan-antibody complex inhaled through non-invasive aerosol inhalation was developed for immunotherapy against lung cancer in mice.[71] Therefore, it is promising for immunotherapy against lung metastasis using a unique aerosol inhalation delivery system for immune checkpoint blockade antibodies, without the concern of systemic toxicity.[71] Additionally, an inhaled

 https://doi.org/10.2147/DDDT.S575392

aerosolized immunotherapeutic DV281 (C-class CpG-ODN) combined with an inhibitor of the anti-programmed cell death protein 1 (PD-1) immune checkpoint was used to treat lung cancer.[72]

However, challenges for inhaled biologics exist in the maintenance of drug stability, manufacture of specialized formulations, and overcoming anatomical barriers within the lungs (1) Maintenance of drug stability is difficult:[73] Biologics such as proteins, peptides, and nucleic acids are highly sensitive to physical and chemical stress. During aerosolization, shear forces, air–liquid interfaces, and exposure to heat or moisture can induce denaturation, aggregation, or loss of biological activity. Long-term storage also poses problems, as many biologics require strict control of temperature and humidity to prevent degradation. (2) Manufacture of specialized formulations for inhalation is technically demanding:[74] Biologics must be formulated into particles with precise aerodynamic diameters (typically 1–5 μm) to ensure deep lung deposition, while preserving molecular integrity. Processes such as spray drying, freeze drying, or jet milling can compromise protein structure or reduce yield. In addition, excipient selection is limited, as additives must be both biocompatible with the lung and capable of stabilizing the biologic during processing and delivery. (3) Anatomical and physiological barriers within the lungs significantly limit effective delivery:[75] Mucus layers, pulmonary surfactants, and alveolar macrophages can trap or clear inhaled biologics before they reach target cells. Enzymatic activity in the lung may further degrade sensitive molecules, and non-uniform airflow can lead to inconsistent regional deposition. Overcoming these barriers remains a major hurdle for successful inhaled biologic therapies.

Nanoparticles and Liposomal Formulations

The inhalable liposomal nanoparticles loaded with antibiotics are an effective method for the treatment of lower respiratory tract infections such as cystic fibrosis, COPD, and bronchiectasis. They have shown significantly higher antibacterial efficacy, and that inhaled antibiotics demonstrate sustained enhancement in lung function in both preclinical and clinical settings are clear[76] (Table 5). Below are examples of the treatment of *Pseudomonas aeruginosa* and *Mycobacterium avium* infections using nanoparticles and liposomal formulations.

Arikace™, a novel formulation of inhaled liposomal amikacin, is an effective therapeutic agent for cystic fibrosis pulmonary infections, because it can penetrate deep within airway secretions and *Pseudomonas aeruginosa* biofilms.[77] Moreover, inhaled liposomal amikacin has been applied in the treatment of pulmonary infections which are difficult to treat.[77]

The efficacy and safety of an amikacin liposome inhalation suspension (ALIS) was evaluated in patients with refractory *Mycobacterium avium* complex (MAC) lung disease.[78] Compared to guideline-based therapy alone, addition of ALIS to standard guideline-based therapy in treating refractory MAC lung disease had greater sputum culture conversion by month 6, and adverse events related to ALIS were generally mild to moderate.[78] A liposomal amikacin inhalation suspension (Arikayce) indicated for MAC lung disease was approved by the US FDA in 2019.[79]

RNA and Target Therapies

The rapidly growing number of studies on RNA therapeutics for pulmonary diseases and the development of inhaled drugs have facilitated the direct delivery of RNA therapeutics to the target site of the lung to minimize systemic exposure.[80] Furthermore, inhaled gene therapy targeting lung diseases has recently attracted increasing interest, and preclinical research is ongoing, although no products have been successfully approved in the market yet[81] (Table 5). Below are examples of the treatment of lung diseases using gene, RNA, and targeted therapies.

Inhaled lipid nanoparticles (LNP) resulted in localized protein production in the lungs of mice and sustained protein production was enhanced through LNP repeated administration, without pulmonary or systemic toxicity.[82] Inhaled LNP-based mRNA encoding cystic fibrosis transmembrane conductance regulator (CFTR) was delivered after nebulization to express the therapeutic pulmonary protein in a CFTR-deficient animal model.[82] This study revealed a feasible design method for the clinical translation of mRNA therapies based on inhalable LNP.[82]

RNA therapies have recently made significant improvement with the approval of Nonpatrol™, an siRNA therapy delivered using a lipid nanoparticle (LNP). LNP-based mRNA vaccines against COVID-19, which were the first mRNA vaccine to be approved on market. Engineering an LNP mRNA formulation to produce a dry powder formulation made it possible to maintain stability and preserve mRNA function compared to liquid formulations.[83] The enhanced green fluorescent protein (eGFP) mRNA loaded spray-dried LNPs which are delivered through the intratracheal route led to the production of eGFP protein. Protein expression detected in cell types involved in adaptive immunity and these cells could be crucial targets for inhaled vaccines against respiratory pathogens.[83] Spray drying of LNPs enhanced their stability and might make RNA deliver to the lung for protein replacement therapy, gene editing, vaccination, etc.[83]

Inhaled Vaccines

Most vaccines are administered by injection to induce potent systemic immunity; however, they are less efficient at triggering mucosal immunity in respiratory tract diseases. Inhaled vaccines induce both mucosal and systemic immune responses, thereby providing rapid and effective protection. Inhaled vaccines can also reduce disease transmission by providing immediate protection against pathogens via the nose or mouth, thereby preventing them from entering the entire body and spreading to other people. However, only a few inhaled vaccines are currently marketed, including a live-attenuated vaccine against influenza and two viral vector vaccines that target SARS-CoV-2 (Table 5).

FluMist®, an intranasal live-attenuated vaccine, is the only nasal spray influenza vaccine approved by the US FDA in 2003. It is a vaccine sprayed into the nose to help protect against influenza in people aged 2–49 years.[84] The advantage of nasally administered vaccines is the induction of local mucosal immune responses, which may block further infection and the broad transmission of respiratory pathogens. This vaccine was demonstrated to induce distinct and compartmentalized antibody responses in mucosa and blood.[85] Mucosal antibodies different from blood antibodies are related to distinct immune responses early post-inoculation, offering protection against mucosal infection.[85]

iNCOVACC® is an intranasal vaccine based on a replication-deficient chimpanzee adenovirus backbone (ChAd36) that expresses the full-length ancestral SARS-CoV-2 S containing two amino acid substitutions in the S2 subunit.[86] Its immunogenicity along with the upregulation of systemic and mucosal immune responses have been evaluated successfully in preclinical studies. Moreover, the induction of a robust systemic immune response has been shown after prime-boost immunizations in clinical trials.[87] However, the vaccine stimulates only a weak upregulation of pre-existing salivary IgA, and actual data on vaccine efficacy are not available.[88] Despite this, iNCOVACC® has been licensed for clinical application in India (2022).

Convidecia Air® is an orally inhaled aerosolized vaccine based on a replication-deficient human type 5 adenovirus (Ad5) vector that expresses the full-length ancestral SARS-CoV-2 spike (S) protein.[89] This aerosolized vaccine is directly inhaled into the patient's airway via a cup dispenser, similar to the natural infection way of the SARS-CoV-2. The heterologous booster regimen with aerosolized Ad5-nCoV is secure and highly immunogenic, boosting both systemic and mucosal immune responses in large-scale population.[90] Aerosolized Ad5-nCoV could provide better protection against SARS-CoV-2 omicron variants than inactivated COVID-19 vaccines.[90] Currently, Convidecia Air® is licensed for clinical applications in China (2022), Morocco (2022), and Indonesia (2023).

Personalized Inhalation Therapy

Inhalation therapy is a major treatment method for various respiratory diseases, and its effectiveness depends on the accuracy of medication delivery. Therefore, personalized inhalation therapy is highly desirable because inhalers should be specifically designed to suit patients' needs (Table 5).

Examples of Cystic Fibrosis Treatment Using Personalized Inhalation Therapy

Three inhaled antibiotics (tobramycin, aztreonam, and colistimethate) have been approved for use in patients with cystic fibrosis as non-biological agents. Inhaled antibiotics are a crucial therapeutic method for cystic fibrosis, because chronic airway infection is a sign of the disease.[91] The development of new formulations of antibiotics and non-antibiotic antimicrobials which may be effective for the treatment of intrinsically antibiotic-resistant organisms has opened a new era of personalized medicine.[91] In a clinical trial in Denmark, it was common to change inhaled antibiotics and use off-label inhaled antibiotics in patients with cystic fibrosis.[92] However, the therapeutic outcomes of personalized antibiotic inhalation prescriptions were satisfactory. Adherence to at least one daily inhalation dose was significantly higher than that to multiple daily inhalations.[92]

Personalized phage therapy is another promising strategy to address antimicrobial-resistant diseases, such as cystic fibrosis, which is probably worsened by recurrent pulmonary infections caused by *Pseudomonas aeruginosa*.[93] In a specific clinical trial, patients (median age, 32 years) with cystic fibrosis were treated with phages in that they were infected with multidrug-resistant or pan-drug-resistant *Pseudomonas*.[93] Personalized nebulized therapy using a phage trade-off strategy might influence clinical and microbiological endpoints, but this has to be evaluated in larger clinical trials.[93]

Discussion on the Success and Challenge of Personalized Inhalation Therapy

Personalized inhalation therapy has emerged as an effective strategy for improving treatment outcomes in chronic respiratory diseases, particularly cystic fibrosis. One major success of this approach lies in the targeted delivery of inhaled antibiotics such as tobramycin, aztreonam, and colistimethate, which achieve high local drug concentrations in the lungs while limiting systemic exposure. Clinical studies have demonstrated that individualized selection and rotation of inhaled antibiotics, including off-label use, can yield satisfactory therapeutic outcomes in patients with chronic airway infections.[92] These findings highlight the clinical value of tailoring antimicrobial therapy based on patient-specific microbiological profiles and treatment responses. Another important success of personalized inhalation therapy is improved treatment adherence. Evidence from the Danish clinical trial indicates that adherence to at least one daily inhalation dose was significantly higher than adherence to multiple daily inhalations.[92] This underscores the importance of considering treatment burden, inhaler design, and dosing frequency when personalizing inhalation regimens. Simplified treatment schedules aligned with patients' daily routines may enhance long-term compliance and, consequently, clinical effectiveness.

Despite of these successes, several challenges remain. Chronic airway infection in cystic fibrosis patients is often caused by intrinsically or acquired antibiotic-resistant organisms, limiting the effectiveness of conventional inhaled antibiotics. Novel antibiotic formulations and non-antibiotic antimicrobials represent a promising extension of personalized medicine, but robust clinical evidence which can support their long-term efficacy is still limited. Additionally, heterogeneity in airway obstruction and mucus accumulation can lead to uneven aerosol deposition, reducing drug delivery to severely affected lung regions.

Personalized phage therapy also provides a novel and highly specific approach to address antimicrobial resistance, particularly in cystic fibrosis patients infected with multidrug- or pandrug-resistant *Pseudomonas aeruginosa*.[93] Early clinical studies suggest that nebulized phage therapy may influence both clinical and microbiological outcomes. However, these findings are only based on small cohorts, larger and controlled trials are required to establish efficacy, optimize dosing strategies, and assess long-term safety.[93]

Although personalized inhalation therapy has demonstrated significant benefits in cystic fibrosis management, further clinical validation and technological optimization are needed to overcome current limitations and enable broader clinical implementation.

Perspectives and Challenges

The delivery of inhalation drugs is transitioning from a niche pulmonary route to a mainstream platform for systemic and precision therapies. As digital, formulation, and biological technologies converge, inhalation will play a vital role in the future of personalized treatments and patient-centric medicine. The future outlook of inhalation drugs includes expansion into non-respiratory indications (eg, central nervous system disorders, diabetes, and lung cancer), the development of next-generation inhalable excipients and stabilizers, integration with wearables and telehealth for chronic disease management, green propellants, and recyclable device components to meet sustainability goals.[94–96] Although inhalation drugs are promising, they still have some challenges and limitations to overcome or evaluate (Table 6).

Conclusions

The delivery of inhalation drugs has evolved beyond the traditional treatment of asthma and COPD, and has become a promising platform for systemic therapies and precision medicine. The pulmonary route offers benefits such as rapid onset, targeted local delivery, reduced systemic side-effects, and avoidance of first-pass metabolism. Emerging trends include smart inhalers integrated with digital technology for adherence monitoring; inhaled biologics, including peptides and monoclonal antibodies; and nanoparticle-based formulations, enabling sustained release and targeted therapy. Inhaled gene and RNA therapies are under development for diseases such as cystic fibrosis and lung cancer, and inhaled vaccines

Table 6 Challenges or Limitations for Inhalation Drugs

Aspect	Challenges or Limitations
Patient adaptation	Inhaled drugs may not suitable for all patients such as elderly and infants
Drug and device compatibility	Not all drugs can be effectively formulated for inhalation Correct use of inhalers is crucial for efficacy
Stability of formulations	Inhaled drugs must remain stable and effective in aerosol form
Pulmonary clearance mechanisms	Mucociliary clearance and alveolar macrophages can remove or degrade inhaled drugs
Tolerance	Repeated usage of inhaled drugs might induce tolerance in some patients
Quantity variability	Actual inhaled quantity may be variable (not fixed) in taking inhaled drugs every time
Inter-patient variability	Lung anatomy and inhalation effort affect inhaled drug deposition
Formulation constraints	Biologics may denature during aerosolization
Side-effect	Some patients may be allergic to inhaled drugs
Environmental impact	Hydrofluoroalkane (HFA) propellants in Metered-Dose Inhalers (MDIs) raise climate concerns
Regulatory and manufacturing considerations	Combination product approval (device + formulation) poses unique regulatory challenges Focus on good inhaler technique training in real-world use Emphasis on device-formulation compatibility in development

are being explored to induce mucosal immunity against pathogens, such as influenza viruses and SARS-CoV-2. Advances in device engineering, including SMIs and DPIs, have enhanced patient usability and dose precision, although challenges and limitations remain (Table 6). The future of inhalation drug delivery is focused on expanding its applications beyond respiratory diseases, integrating AI for personalized treatment, developing greener technologies, and combining wearable devices for remote disease management. Overall, inhalation therapy plays an important role in the next generation of patient-centric and precise healthcare.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bamgbade OA, Richards RN, Mwaba M, Ajirenike RN, Metekia LM, Olatunji BT. Facial topical cream promotes facemask tolerability and compliance during COVID-19 pandemic. *J Taibah Univ Med Sci*. 2022;17(3):441–447. doi:10.1016/j.jtumed.2021.12.012. Epub 2022 Feb 26.
2. Leppert W, Malec-Milewska M, Zajaczkowska R, Wordliczek J. Transdermal and Topical Drug Administration in the Treatment of Pain. *Molecules*. 2018;23(3):681. doi:10.3390/molecules23030681
3. Wong WF, Ang KP, Sethi G, Looi CY. Recent Advancement of Medical Patch for Transdermal Drug Delivery. *Medicina*. 2023;59(4):778. doi:10.3390/medicina59040778
4. Al Hanbali OA, Khan HMS, Sarfraz M, Arafat M, Ijaz S, Hameed A. Transdermal patches: design and current approaches to painless drug delivery. *Acta Pharm*. 2019;69(2):197–215. doi:10.2478/acph-2019-0016
5. Deng B, Liu S, Wang Y, et al. Oral Nanomedicine: challenges and Opportunities. *Adv Mater*. 2024;36(6):e2306081. doi:10.1002/adma.202306081. Epub 2023 Nov 30.
6. McConville JT. Current developments in oral drug administration. *Drug Dev Ind Pharm*. 2017;43(5):699. doi:10.1080/03639045.2017.1290865
7. Kim JY, Kim J, Lee M. Are virtual reality intravenous injection training programs effective for nurses and nursing students? A systematic review. *Nurse Educ Today*. 2024;139:106208. doi:10.1016/j.nedt.2024.106208. Epub 2024 Apr 11.
8. Hayes C, Williamson L. Injection technique. Intravenous--1. *Nurs Times*. 1998;94(45):1–2.
9. Ayinde O, Hayward RS, Ross JDC. The effect of intramuscular injection technique on injection associated pain; a systematic review and meta-analysis. *PLoS One*. 2021;16(5):e0250883. doi:10.1371/journal.pone.0250883. eCollection 2021.
10. Shaw H. Intramuscular injection. *Nurs Stand*. 2015;30(6):61–62. doi:10.7748/ns.30.6.61. s48.
11. Usach I, Martinez R, Festini T, Peris JE. Subcutaneous Injection of Drugs: literature Review of Factors Influencing Pain Sensation at the Injection Site. *Adv Ther*. 2019;36(11):2986–2996. doi:10.1007/s12325-019-01101-6. Epub 2019 Oct 5.
12. Ogston-Tuck S. Subcutaneous injection technique: an evidence-based approach. *Nurs Stand*. 2014;29(3):53–58. doi:10.7748/ns.29.3.53.e9183

13. Ahmed Saeed Al-Japairai K, Mahmood S, Hamed Almurisi S, et al. Current trends in polymer microneedle for transdermal drug delivery. *Int J Pharm*. 2020;587:119673. doi:10.1016/j.ijpharm.2020.119673. Epub 2020 Jul 30.
14. Nguyen HX, Nguyen CN. Microneedle-Mediated Transdermal Delivery of Biopharmaceuticals. *Pharmaceutics*. 2023;15(1):277. doi:10.3390/pharmaceutics15010277
15. Leach CL. Inhalation aspects of therapeutic aerosols. *Toxicol Pathol*. 2007;35(1):23–26. doi:10.1080/01926230601072335
16. Devillier P, Salvator H, Roche N. The choice of inhalation device: a medical act. *Rev Mal Respir*. 2015;32(6):599–607. doi:10.1016/j.rmr.2014.10.729. Epub 2014 Nov 6.
17. Choudhury H, Gorain B, Chatterjee B, Mandal UK, Sengupta P, Tekade RK. Pharmacokinetic and Pharmacodynamic Features of Nanoemulsion Following Oral, Intravenous, Topical and Nasal Route. *Curr Pharm Des*. 2017;23(17):2504–2531. doi:10.2174/1381612822666161201143600
18. Holloway M. Route of administration for erythropoiesis-stimulating agents: patient and nursing considerations. *Nephrol Nurs J*. 2007;34(5):527–531.
19. Beyssac E. The unusual routes of administration. *Eur J Drug Metab Pharmacokinet*. 1996;21(2):181–187. doi:10.1007/BF03190268
20. Birkhäuser MH, Haenggi W. Benefits of different routes of administration. *Int J Fertil Menopausal Stud*. 1994;39(1):11–19.
21. Jones H, Lawton A, Gupta A. Asthma Attacks in Children-Challenges and Opportunities. *Indian J Pediatr*. 2022;89(4):373–377. doi:10.1007/s12098-021-04069-w. Epub 2022 Jan 21.
22. Bosi A, Tonelli R, Castaniere I, Clini E, Beghè B. Acute severe asthma: management and treatment. *Minerva Med*. 2021;112(5):605–614. doi:10.23736/S0026-4806.21.07372-9. Epub 2021 Feb 26.
23. Turégano-Yedro M, Trillo-Calvo E, Navarro IRF, Jd M-V. Inhaler Adherence in COPD: a Crucial Step Towards the Correct Treatment. *Int J Chron Obstruct Pulmon Dis*. 2023;18:2887–2893. doi:10.2147/COPD.S431829. eCollection 2023.
24. Møller R, Pressler T, Qvist T. Antimicrobial Strategies for Cystic Fibrosis. *Semin Respir Crit Care Med*. 2023;44(2):297–306. doi:10.1055/s-0042-1758733. Epub 2022 Dec 19.
25. Bafadhel M, Faner R, Taillé C, et al. Inhaled corticosteroids for the treatment of COVID-19. *Eur Respir Rev*. 2022;31(166):220099. doi:10.1183/16000617.0099-2022. Print 2022 Dec 31.
26. Van Heeke G, Allosery K, De Brabandere V, De Smedt T, Detalle L, de Fougerolles A. Nanobodies as inhaled biotherapeutics for lung diseases. *Pharmacol Ther*. 2017;169:47–56. doi:10.1016/j.pharmthera.2016.06.012. Epub 2016 Jun 29.
27. Subramanian J, Dhand R. Inhaled Chemotherapy. *J Aerosol Med Pulm Drug Deliv*. 2025;38(2):90–101. doi:10.1089/jamp.2025.19211.js
28. Chung SW, Hil-lal TA, Byun Y. Strategies for non-invasive delivery of biologics. *J Drug Target*. 2012;20(6):481–501. doi:10.3109/1061186X.2012.693499. Epub 2012 May 28.
29. Kumbhar P, Manjappa A, Shah R, et al. Inhalation delivery of repurposed drugs for lung cancer: approaches, benefits and challenges. *J Control Release*. 2022;341:1–15. doi:10.1016/j.jconrel.2021.11.015. Epub 2021 Nov 13.
30. Jaijyan DK, Selariu A, Cruz-Cosme R, et al. New intranasal and injectable gene therapy for healthy life extension. *Proc Natl Acad Sci U S A*. 2022;119(20):e2121499119. doi:10.1073/pnas.2121499119. Epub 2022.
31. Jeyanathan M, Afkhami S, Kang A, Xing Z. Viral-vectored respiratory mucosal vaccine strategies. *Curr Opin Immunol*. 2023;84:102370. doi:10.1016/j.coi.2023.102370
32. Heida R, Hinrichs WL, Frijlink HW. Inhaled vaccine delivery in the combat against respiratory viruses: a 2021 overview of recent developments and implications for COVID-19. *Expert Rev Vaccines*. 2022;21(7):957–974. doi:10.1080/14760584.2021.1903878
33. Mettelman RC, Allen EK, Thomas PG. Mucosal immune responses to infection and vaccination in the respiratory tract. *Immunity*. 2022;55:749–780. doi:10.1016/j.immuni.2022.04.013
34. Loo CY, Lee WH, Zhou QT. Recent Advances in Inhaled Nanoformulations of Vaccines and Therapeutics Targeting Respiratory Viral Infections. *Pharma Res*. 2023;40:1015–1036. doi:10.1007/s11095-023-03520-1
35. Stylianou E, Satti I, Stylianou E, Satti I. Inhaled aerosol viral-vectored vaccines against tuberculosis. *Curr Opin Virol*. 2024;66:101408. doi:10.1016/j.coviro.2024.101408
36. Tscherne A, Krammer F. A review of currently licensed mucosal COVID-19 vaccines. *Vaccine*. 2025;61:127356. doi:10.1016/j.vaccine.2025.127356. Online ahead of print.
37. Fink JB, Stapleton KW. Nebulizers. *J Aerosol Med Pulm Drug Deliv*. 2024;37(3):140–156. doi:10.1089/jamp.2024.29110.jbf. Epub 2024.
38. Sadeghi T, Fatehi P, Pakzad L. Effect of Nasal Inhalation on Drug Particle Deposition and Size Distribution in the Upper Airway: with Soft Mist Inhalers. *Ann Biomed Eng*. 2024;52(5):1195–1212. doi:10.1007/s10439-023-03423-7. Epub 2024 Mar 20.
39. Calmet H, Inthavong K, Eguzkitza B, Lehmkuhl O, Houzeaux G, Vázquez M. Nasal sprayed particle deposition in a human nasal cavity under different inhalation conditions. *PLoS One*. 2019;14(9):e0221330. doi:10.1371/journal.pone.0221330. eCollection 2019.
40. Doub WH, Suman JM, Copley M, Goodey AP, Hosseini S, Mitchell JP. Laboratory Performance Testing of Aqueous Nasal Inhalation Products for Droplet/Particle Size Distribution: an Assessment from the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). *AAPS Pharm Sci Tech*. 2023;24(7):208. doi:10.1208/s12249-023-02665-x
41. Inthavong K, Ma J, Shang Y, et al. Geometry and airflow dynamics analysis in the nasal cavity during inhalation. *Clin Biomech*. 2019;66:97–106. doi:10.1016/j.clinbiomech.2017.10.006. Epub 2017 Oct 7.
42. Fröhlich E, Salar-Behzadi S. Oral inhalation for delivery of proteins and peptides to the lungs. *Eur J Pharm Biopharm*. 2021;163:198–211. doi:10.1016/j.ejpb.2021.04.003. Epub 2021 Apr 11.
43. Cox DP, Ferreira L. The Oral Effects of Inhalation Corticosteroid Therapy: an Update. *J Calif Dent Assoc*. 2017;45(5):227–233.
44. Mitchell JP, Nagel MW. Oral inhalation therapy: meeting the challenge of developing more patient-appropriate devices. *Expert Rev Med Devices*. 2009;6(2):147–155. doi:10.1586/17434440.6.2.147
45. de Kruijf W, Ehrhardt C. Inhalation delivery of complex drugs-the next steps. *Curr Opin Pharmacol*. 2017;36:52–57. doi:10.1016/j.coph.2017.07.015. Epub 2017 Aug 30.
46. Gurumurthy A, Kleinstreuer C. Analysis of improved oral drug delivery with different helical stream inhalation modes. *Comput Biol Med*. 2022;141:105132. doi:10.1016/j.compbiomed.2021.105132. Epub 2021 Dec 23.
47. Fernandes SD, Koland M. Understanding the Essentialities in Establishing the Bioequivalence of Oral Inhalation Drug Products to be Marketed in the USA. *Ther Innov Regul Sci*. 2020;54(4):738–748. doi:10.1007/s43441-019-00007-3. Epub 2019 Dec 6.

48. MacLoughlin R, Martin-Loeches I. Not all nebulizers are created equal: considerations in choosing a nbulizer for aerosol delivery during mechanical ventilation.Expert. *Rev Respir Med*. 2023;17(2):131–142. doi:10.1080/17476348.2023.2183194. Epub 2023 Feb 27.
49. Martin AR, Finlay WH. Nebulizers for drug delivery to the lungs. *Expert Opin Drug Deliv*. 2015;12(6):889–900. doi:10.1517/17425247.2015.995087. Epub 2014 Dec 23.
50. Barjaktarevic IZ, Milstone AP. Nebulized Therapies in COPD: past, Present, and the Future. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1665–1677. doi:10.2147/COPD.S252435. eCollection.
51. Morton DAV, Barling D. Developing Dry Powder Inhaler Formulations. *J Aerosol Med Pulm Drug Deliv*. 2024;37(2):90–99. doi:10.1089/jamp.2024.29109.davm
52. Gaikwad SS, Pathare SR, More MA, et al. Dry Powder Inhaler with the technical and practical obstacles, and forthcoming platform strategies. *J Control Release*. 2023;355:292–311. doi:10.1016/j.jconrel.2023.01.083. Epub 2023 Feb 9.
53. Hasan SS, Capstick T, Zaidi STR, Kow CS, Merchant HA. Use of corticosteroids in asthma and COPD patients with or without COVID-19. *Respir Med*. 2020;170:106045. doi:10.1016/j.rmed.2020.106045. Epub 2020 May 26.
54. Vallorz E, Sheth P, Myrdal P. Pressurized Metered Dose Inhaler Technology: manufacturing. *AAPS Pharm Sci Tech*. 2019;20(5):177. doi:10.1208/s12249-019-1389-9
55. Ivey JW, Vehring R, Finlay WH. Understanding pressurized metered dose inhaler performance. *Expert Opin Drug Deliv*. 2015;12(6):901–916. doi:10.1517/17425247.2015.984683. Epub 2014 Dec 13.
56. Komalla V, Wong CYJ, Sibum I, et al. Advances in soft mist inhalers. *Expert Opin Drug Deliv*. 2023;20(8):1055–1070. doi:10.1080/17425247.2023.2231850. Epub 2023.
57. Hänsel M, Bambach T, Wachtel H. Reduced Environmental Impact of the Reusable Respimat® Soft Mist Inhaler Compared with Pressurised Metered-Dose Inhalers. *Adv Ther*. 2019;36(9):2487–2492. doi:10.1007/s12325-019-01028-y. Epub 2019 Jul 17.
58. Sorino C, Negri S, Spanevello A, Visca D, Scichilone N. Inhalation therapy devices for the treatment of obstructive lung diseases: the history of inhalers towards the ideal inhaler. *Eur J Intern Med*. 2020;75:15–18. doi:10.1016/j.ejim.2020.02.023. Epub 2020 Feb 26.
59. Lipson DA, Barnhart F, Brealey N, et al. IMPACT Investigators. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med*. 2018;378(18):1671–1680. doi:10.1056/NEJMoa1713901. Epub 2018 Apr 18.
60. Lipson DA, Barnacle H, Birk R, et al. FULFIL Trial: once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2017;196(4):438–446. doi:10.1164/rccm.201703-0449OC
61. Levy ML, Kocks JWH, Bosnic-Anticevich S, et al. Uncovering patterns of inhaler technique and reliever use: the value of objective, personalized data from a digital inhaler. *NPJ Prim Care Respir Med*. 2024;34(1):23. doi:10.1038/s41533-024-00382-x
62. Mosnaim GS, Hoyte FCL, Safioti G, et al. Effectiveness of a Maintenance and Reliever Digihaler System in Asthma: 24-Week Randomized Study (CONNECT2). *J Allergy Clin Immunol Pract*. 2024;12(2):385–395.e4. doi:10.1016/j.jaip.2023.11.037. Epub 2023 Nov 30.
63. Feldman GJ, Sousa AR, Lipson DA, et al. Comparative Efficacy of Once-Daily Umeclidinium/Vilanterol and Tiotropium/Olodaterol Therapy in Symptomatic Chronic Obstructive Pulmonary Disease: a Randomized Study. *Adv Ther*. 2017;34(11):2518–2533. doi:10.1007/s12325-017-0626-4. Epub 2017 Nov 1.
64. Thomas L. What are Smart Inhalers? News Medical Life Sciences. Available from: https://www.news-medical.net/health/What-are-Smart-Inhalers.aspx. Accessed Jun 6, 2023.
65. Mohammadi D. Smart inhalers: will they help to improve asthma care? *Pharm J*. 2017;298:7900
66. Dierick BJH, Achterbosch M, Eikholt AA, et al. Electronic monitoring with a digital smart spacer to support personalized inhaler use education in patients with asthma: the randomized controlled OUTERSPACE trial. *Respir Med*. 2023;218:107376. doi:10.1016/j.rmed.2023.107376. Epub 2023 Aug 6.
67. Cruz-Teran C, Tiruthani K, McSweeney M, Ma A, Pickles R, Lai SK. Challenges and opportunities for antiviral monoclonal antibodies as COVID-19 therapy. *Adv Drug Deliv Rev*. 2021;169:100–117. doi:10.1016/j.addr.2020.12.004. Epub 2020 Dec 9.
68. Ameratunga R, Jordan A, Lehnert K, et al. SARS-CoV-2 evolution has increased resistance to monoclonal antibodies and first-generation COVID-19 vaccines: is there a future therapeutic role for soluble ACE2 receptors for COVID-19? *Antiviral Res*. 2024;227:105894. doi:10.1016/j.antiviral.2024.105894. Epub 2024 Apr 25.
69. Kaduszkiewicz H, Kochen MM, Kluge S, Malin JJ, Weibel S, Skoetz N, Guideline Group. Recommendations for the Outpatient Drug Treatment of Patients With COVID-19. *Dtsch Arztebl Int*. 2022;119(19):342–349. doi:10.3238/arztebl.m2022.0203
70. Maillet A, Guilleminault L, Lemarié E, et al. The airways, a novel route for delivering monoclonal antibodies to treat lung tumors. *Pharm Res*. 2011;28(9):2147–2156. doi:10.1007/s11095-011-0442-5. Epub 2011 Apr 14.
71. Jin Q, Zhu W, Zhu J, et al. Nanoparticle-Mediated Delivery of Inhaled Immunotherapeutics for Treating Lung Metastasis. *Adv Mater*. 2021;33(7):e2007557. doi:10.1002/adma.202007557. Epub 2021 Jan 14.
72. Kell SA, Kachura MA, Renn A, Traquina P, Coffman RL, Campbell JD. Preclinical development of the TLR9 agonist DV281 as an inhaled aerosolized immunotherapeutic for lung cancer: pharmacological profile in mice, non-human primates, and human primary cells. *Int Immunopharmacol*. 2019;66:296–308. doi:10.1016/j.intimp.2018.11.019. Epub 2018 Nov 29.
73. Chang RYK, Chan HK. Advancements in Particle Engineering for Inhalation Delivery of Small Molecules and Biotherapeutics. *Pharm Res*. 2022;39(12):3047–3061. doi:10.1007/s11095-022-03363-2. Epub 2022 Sep 7.
74. Chang RYK, Chow MYT, Khanal D, Chen D, Chan HK. Dry powder pharmaceutical biologics for inhalation therapy. *Adv Drug Deliv Rev*. 2021;172:64–79. doi:10.1016/j.addr.2021.02.017. Epub 2021 Mar 8.
75. Liang W, Pan HW, Vllasaliu D, Lam JKW. Pulmonary Delivery of Biological Drugs. *Pharmaceutics*. 2020;12(11):1025. doi:10.3390/pharmaceutics12111025
76. Panthi VK, Fairfull-Smith KE, Islam N. Antibiotic loaded inhalable liposomal nanoparticles against lower respiratory tract infections: challenges, recent advances, and future perspectives. *J Drug Delivery Sci Technol*. 2024;2024:S1773224724001850.
77. Waters V, Ratjen F. Inhaled liposomal amikacin. *Expert Rev Respir Med*. 2014;8(4):401–409. doi:10.1586/17476348.2014.918507. Epub 2014 May 31.
78. Griffith DE, Eagle G, Thomson R, et al. CONVERT Study Group. Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by *Mycobacterium avium* Complex (CONVERT). A Prospective, Open-Label, Randomized Study. *Am J Respir Crit Care Med*. 2018;198(12):1559–1569. doi:10.1164/rccm.201807-1318OC
79. Kaufman MB. Pharmaceutical Approval Update. *PT*. 2019;44(2):42–44.

80. Chow MYT, Qiu Y, Lam JKW. Inhaled RNA Therapy: from Promise to Reality. *Trends Pharmacol Sci*. 2020;41(10):715–729. doi:10.1016/j.tips.2020.08.002. Epub 2020 Sep 4.
81. Ruzycki CA, Montoya D, Irshad H, et al. Inhalation delivery of nucleic acid gene therapies in preclinical drug development. *Expert Opin Drug Deliv*. 2023;20(8):1097–1113. doi:10.1080/17425247.2023.2261369. Epub 2023 Oct 16.
82. Kim J, Jozic A, Lin Y, et al. Engineering Lipid Nanoparticles for Enhanced Intracellular Delivery of mRNA through Inhalation. *ACS Nano*. 2022;16(9):14792–14806. doi:10.1021/acsnano.2c05647. Epub 2022 Aug 29.
83. Friis KP, Gracin S, Oag S, et al. Spray dried lipid nanoparticle formulations enable intratracheal delivery of mRNA. *J Control Release*. 2023;363:389–401. doi:10.1016/j.jconrel.2023.09.031. Epub 2023 Sep 30.
84. Influenza vaccine for 2024-2025. *Med Lett Drugs Ther*. 2024;66(1711):145–150. doi:10.58347/tml.2024.1711a
85. Thwaites RS, Uruchurtu ASS, Negri VA, et al. Early mucosal events promote distinct mucosal and systemic antibody responses to live attenuated influenza vaccine. *Nat Commun*. 2023;14(1):8053. doi:10.1038/s41467-023-43842-7
86. Sunagar R, Prasad SD, Ella R, Vadrevu KM. Preclinical evaluation of safety and immunogenicity of a primary series intranasal COVID-19 vaccine candidate (BBV154) and humoral immunogenicity evaluation of a heterologous prime-boost strategy with COVAXIN (BBV152). *Front Immunol*. 2022;13:1063679. doi:10.3389/fimmu.2022.1063679
87. Akula VR, Bhate AS, Gillurkar CS, et al. BBV154 Study Group. Effect of heterologous intranasal iNCOVACC() vaccination as a booster to two-dose intramuscular Covid-19 vaccination series: a randomized Phase 3 clinical trial. *Commun Med (Lond)*. 2025;5(1):133. doi:10.1038/s43856-025-00818-6
88. Tscherne A, Krammer F. A review of currently licensed mucosal COVID-19 vaccines. *Vaccine*. 2025;61:127356. doi:10.1016/j.vaccine.2025.127356. Epub 2025 Jun 6.
89. Wang F, Huang B, Deng Y, Zhang S, Liu X, Liu Q. Neutralizing antibody levels associated with injectable and aerosolized Ad5-nCoV boosters and BA.2 infection. *BMC Med*. 2023;21(1):233. doi:10.1186/s12916-023-02942-3
90. Li JX, Hou LH, Gou JB, et al. Six-Province COVID-19 Vaccine Study Group. Safety, immunogenicity and protection of heterologous boost with an aerosolised Ad5-nCoV after two-dose inactivated COVID-19 vaccines in adults: a multicentre, open-label phase 3 trial. *Lancet Infect Dis*. 2023;23(10):1143–1152. doi:10.1016/S1473-3099(23)00350-X. Epub 2023 Jun 20. PMID: 37352880 Clinical Trial
91. Biller JA. Inhaled antibiotics: the new era of personalized medicine? *Curr Opin Pulm Med*. 2015;21(6):596–601. doi:10.1097/MCP.0000000000000216
92. Møller R, Nielsen BU, Faurholt-Jepsen D, et al. Use of inhaled antibiotics among Danish patients with cystic fibrosis. *Qvist T Pediatr Pulmonol*. 2022;57(7):1726–1734. doi:10.1002/ppul.25942. Epub 2022 May 14.
93. Chan BK, Stanley GL, Kortright KE, et al. Personalized inhaled bacteriophage therapy for treatment of multidrug-resistant Pseudomonas aeruginosa in cystic fibrosis. *Nat Med*. 2025;31(5):1494–1501. doi:10.1038/s41591-025-03678-8. Epub 2025 Apr 29.
94. Kikidis D, Konstantinos V, Tzovaras D, Usmani OS. The Digital Asthma Patient: the History and Future of Inhaler Based Health Monitoring Devices. *J Aerosol Med Pulm Drug Deliv*. 2016;29(3):219–232. doi:10.1089/jamp.2015.1267. Epub 2016 Feb 26.
95. Koehorst-ter Huurne K, Movig K, van der Valk P, van der Palen J, Brusse-Keizer M. The influence of type of inhalation device on adherence of COPD patients to inhaled medication. *Expert Opin Drug Deliv*. 2016;13(4):469–475. doi:10.1517/17425247.2016.1130695. Epub 2016 Jan 4.
96. Dhanjal DS, Sharma P, Mehta M, et al. Concepts of advanced therapeutic delivery systems for the management of remodeling and inflammation in airway diseases. *Future Med Chem*. 2022;14(4):271–288. doi:10.4155/fmc-2021-0081. Epub 2022 Jan 12.