www.ijarp.com ISSN 2456-9992 Page: 01-30

International Journal Advanced Research Publications

Review Article

Volume: 02
Issue: 05

PULMONARY DRUG DELIVERY SYSTEMS: MECHANISMS, FORMULATION STRATEGIES, DEVICE TECHNOLOGIES, AND EMERGING FRONTIERS

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Article Received: 11 April 2026, Article Revised: 01 May 2026, Published on: 21 May 2026

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DOI: https://doi-doi.org/101555/ijarp.5276

ABSTRACT:

One of the most advanced and therapeutically important medication delivery methods is pulmonary drug delivery. The pulmonary route is perfect for both local and systemic drug delivery because it provides unmatched access to the vast alveolar surface area (~140 m2), thin air–blood barrier (~0.2–0.5 µm), abundant vascularization, and avoidance of hepatic first-pass metabolism. The anatomical and physiological underpinnings of pulmonary medication delivery are methodically examined in this thorough overview, which also highlights the crucial role that aerosol particle properties like aerodynamic diameter, density, and shape play.the entire range of inhaler device technologies, including jet and mesh nebulizers, soft mist inhalers (SMIs), pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and advanced formulation techniques like liposomes, polymeric nanoparticles, PLGA microspheres, solid lipid nanoparticles (SLNs), dendrimers, and new exosome-based carriers. We also go over the pharmacokinetics and pharmacodynamics of inhaled medications, clinical uses in lung cancer, asthma, cystic fibrosis, pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), and systemic diseases like diabetes. The use of artificial intelligence in device design, intelligent and stimuli-responsive delivery systems, regulatory frameworks controlling inhaled products, and important issues like mucociliary clearance, macrophage phagocytosis, patient adherence, and environmental sustainability are all given particular attention. An outlook for gene therapy, mRNA delivery, personalized medicine, and digital health integration is included in the review's conclusion. To assist researchers in creating this material, a carefully selected list of 50 foundational references is offered.

INDEX TERMS: COPD, asthma, liposomes, mucociliary clearance, targeted lung delivery, smart inhalers, gene therapy, inhaled medications, aerosol medicine, dry powder inhalers, and nanoparticle formulations.

I. INTRODUCTION

One of the easiest and most beneficial pharmacological gateways for drug delivery is the respiratory system. In the modern period, the pulmonary route—long utilized by medical professionals through rudimentary tools like opium pipes and herbal fumigations—has been polished into a precise science of aerosol therapy. The standard of care for hundreds of millions of patients worldwide who suffer from infectious pulmonary conditions, obstructive and restrictive lung diseases, and increasingly systemic diseases for which the lung offers a better absorption gateway than oral or parenteral routes is now supported by pulmonary drug delivery systems (PDDS)

The pulmonary route is appealing due to a number of physiological and anatomical benefits. When alveoli are fully extended, the human lung has a total surface area of around 70–140 m^2. The alveolar epithelium is just 0.1–0.5 μm thick and is distributed across a dense capillary network that receives all of the cardiac output. In terms of onset speed, drug molecules deposited on the alveolar surface can enter the systemic circulation in a matter of seconds, outperforming intravenous injection while removing the dangers of venipuncture. Concurrently, direct administration to the illness site significantly reduces the systemic dose needed for locally acting medications like bronchodilators and inhaled corticosteroids, minimizing side effects.

Inhaled medication delivery is still technically challenging despite these benefits. Each of the 23 bifurcation generations in the convoluted airway tree that the aerosol must traverse presents conflicting deposition mechanisms such as Brownian diffusion, gravity sedimentation, and inertial impaction. The fraction of the nominal dose that eventually reaches the target lung region is determined by the interaction of particle engineering, device design, formulation chemistry, and patient technique. There are still significant inefficiencies: state-of-the-art devices may transport 50–80% of the emitted dose to the lungs, whereas typical pMDIs without spacers only deliver 10–20%. The therapeutic and commercial significance of this sector is highlighted by the global pulmonary medication delivery market. The market, which was valued at about USD 39.8 billion in 2020, is expected to grow to USD 85.9 billion by 2030 (CAGR ~8.0%), driven by the proliferation of smart, connected inhaler technologies, new biological therapeutics looking for a non-invasive delivery method,

and rising respiratory disease burdens. Further broadening the therapeutic potential of pulmonary administration, the COVID-19 pandemic has also sparked research into inhaled antiviral and vaccine formulations.

For researchers, pharmacists, and biomedical engineers working on the development, improvement, and clinical implementation of pulmonary drug delivery systems, this review seeks to be an authoritative resource. From pulmonary anatomy and aerosol physics to device engineering and formulation science, clinical data, regulatory needs, and future goals, it covers the entire scientific spectrum.

II. PHYSIOLOGY AND PULMONARY ANATOMY RELATED TO DRUG DELIVERY

A. The Respiratory Tract's Structure

The upper respiratory tract, which includes the nasal cavity, nasopharynx, and larynx, and the lower respiratory tract, which further subdivides into the respiratory zone (respiratory bronchioles, alveolar ducts, and alveolar sacs, generations 17–23) and the conducting zone (trachea through terminal bronchioles, generations 0–16). Each division offers unique biological obstacles and physicochemical microenvironments that affect the fate of drugs after inhalation

In adults, the trachea (generation 0) has an interior diameter of around 18 mm and gradually tapers through a series of bifurcations. The diameter has decreased to about 0.6 mm by the terminal bronchioles (generation 16), while the respiratory zone’s alveolar ducts and sacs reach as small as 0.3 mm. However, in the distal lung, the cross-sectional area summed over all parallel airways increases significantly, decreasing air velocity and promoting therapeutic aerosol gravitational deposition.

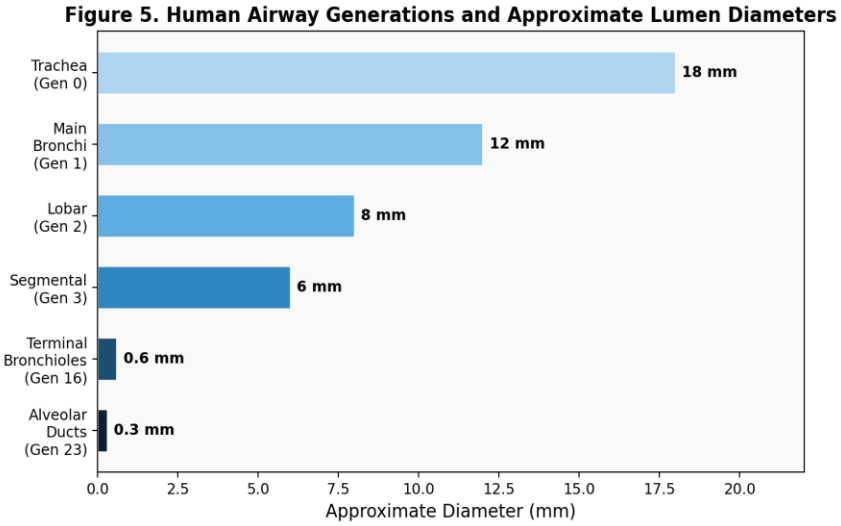

Fig. 5. Approximate lumen diameters across human airway generations. Drug particles must navigate this branching architecture to achieve target site deposition.

Pseudostratified ciliated columnar epithelium covers a gel-on-sol mucus bilayer that lines the mucosal surface of the conducting airways. Mucus is secreted by goblet cells and submucosal glands at a rate of around 10–100 mL per day. Coordinated ciliary beating at about 15 Hz continuously propels the mucus toward the larynx. This mucociliary escalator serves as the main clearance barrier for inhaled particles in the conducting zone, despite being an essential natural defensive system. On the other hand, a thin aqueous hypophase and pulmonary surfactant monolayer cover type I pneumocytes (>95% of surface area, extremely thin) and type II pneumocytes (surfactant secreting) that make up the alveolar epithelium.

B. The Function of Pulmonary Surfactant in Drug Absorption:

Pulmonary surfactant, a complex lipoprotein combination consisting primarily of dipalmitoylphosphatidylcholine (DPPC, ~40% by weight), other phospholipids (~40%), neutral lipids (~10%), and surfactant proteins (SP-A, SP-B, SP-C, SP-D, 5–10%), stabilizes the alveolar air–liquid interface. Surfactants are primarily used to avoid alveolar collapse by reducing surface tension to almost zero at the conclusion of expiration. Surfactant, however, also has a significant impact on inhaled drug particles: it quickly coats deposited particles, makes it easier for them to disperse, modifies the kinetics of disintegration, and, in the case of lipid-based formulations, may encourage membrane fusion and transcytosis. By opsonizing foreign particles for macrophage phagocytosis, which is a crucial clearance mechanism for nanoparticle drug carriers, SP-A and SP-D further contribute to innate immune surveillance.

C. Immunological Barriers and Alveolar Macrophages

The primary cellular defense of the alveolar space is provided by alveolar macrophages (AMs), which are produced from circulating monocytes and sustained by local proliferation. AMs are a significant clearance mechanism for inhaled drug carriers because they efficiently phagocytose particles larger than 1-2 μm in diameter. Particles of sizes between 0.1 and 1.0 μm can pass through the alveolar epithelium by diffusion or transcytosis and are comparatively resistant to AM phagocytosis. Surface PEGylation (stealth nanoparticles), surface decorating with CD47 "don't eat me" signals, and geometric elongation of particles to decrease normalized phagocytic uptake are methods to avoid AM phagocytosis.

D. Inhaled Drug Pharmacokinetics

The interaction of deposition site, dissolving rate, mucociliary clearance, alveolar macrophage clearance, epithelial permeability, and pulmonary metabolism determines the pharmacokinetic fate of an inhaled medication. Due to restricted membrane permeability, hydrophilic small molecules absorb slowly from the alveoli (half-life of hours), but lipophilic molecules move quickly through the alveolar epithelium (minutes). Certain medications may have limited systemic bioavailability due to pulmonary metabolism, which is mediated by CYP450 enzymes (particularly CYP1A1, CYP1B1, and CYP2J2), flavin-containing monooxygenases, and glutathione-S-transferases expressed in Clara cells and pneumocytes. However, this can be used to create pulmonary prodrugs that are activated exclusively in lung tissue.

In healthy people, the epithelial lining fluid (ELF) has a volume of around 25–70 mL with a pH of about 6.9 in the conducting airways and about 7.0–7.4 in the alveoli. Because of this comparatively limited fluid volume, even low drug dosages might momentarily produce extremely high local concentrations. Drug stability and release kinetics for particle formulations are also influenced by the composition of ELF, including its protein content (albumin, immunoglobulins), enzymatic activity, and viscosity.

III. PARTICLE DEPOSITION MECHANISMS AND AEROSOL PHYSICS

A. Mass Median Aerodynamic Diameter and Aerodynamic Diameter

The diameter of a unit-density sphere with the same settling velocity as the inhaled particle is known as the aerodynamic diameter (da). It is the most crucial factor in predicting lung regional deposition. The mass median aerodynamic diameter (MMAD), which is always supplied alongside the geometric standard deviation (GSD) to describe the width of the size

distribution, is the value at which 50% of the aerosol mass is contained in particles with da smaller than that value. The dose available for lower respiratory tract deposition is determined by the respirable fraction, which is often described by several pharmacopeias as particles with da < 5 μm

..Physical dimension (dp), particle density (ρp), and dynamic shape factor (χ) are related as follows:

Where $\rho_0 = 1$ g/cm³ (unit density), $da = dp \cdot \sqrt{(\rho p / \rho_0 \cdot 1/\chi)}$. This equation has significant significance for particle engineering since it permits bigger geometric dimensions while preserving advantageous aerodynamic behavior by lowering particle density (for example, by creating porous particles). Although they are too big for effective AM phagocytosis, porous particles with geometric diameters of 5–20 μm and densities of 0.05–0.4 g/cm³ show MMADs in the respirable range—a sophisticated tactic used in large porous particle (LPP) platforms.

B. Mechanisms of Deposition

Particle deposition in the respiratory tract is governed by three main mechanisms: (1) Inertial impaction dominates for particles larger than 5 μm in high-velocity, high-curvature flow regions like the oropharynx and large bronchi, causing undesired upper airway deposition and serving as the primary loss mechanism for suboptimally engineered aerosols; (2) Gravitational sedimentation becomes significant for particles between 0.5 and 5 μm in the slower-moving peripheral airways, where the settling time is similar to inspiration; strategies that use slow inhalation and breath-holding.

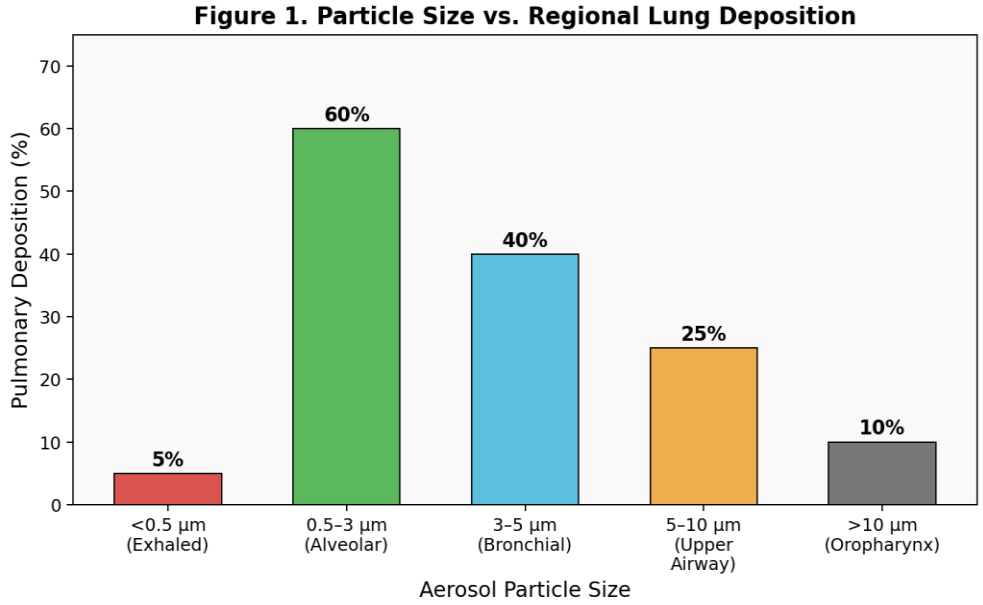

Fig. 1. Regional pulmonary deposition efficiency as a function of aerodynamic particle diameter. Optimal alveolar deposition occurs for particles in the 0.5–3 µm range. Data adapted from ICRP (1994) and Patton & Byron (2007).

For charged aerosols produced by certain nebulizers and charge-modulated DPIs, a fourth mechanism electrostatic precipitation is pertinent. Under healthy settings, the lung airways have a negative surface charge; positively charged particles are more electrostatically attracted to the walls of the airways. Depending on the charge magnitude and particle size, this can either increase oropharyngeal loss or improve targeted deposition.

C. Hygroscopic Development and Its Effects

The majority of pharmaceutical aerosols are produced in settings with relative humidity (RH) far lower than the respiratory tract's (99% RH at body temperature). Hygroscopic particles enlarge prior to arriving at their intended deposition place after absorbing water vapor through inhaling. This expansion may be small (10–30%) for crystalline drug particles, while growth factors of 2–5 can move an aerosol's MMAD into a whole other deposition region for hygroscopic excipients such mannitol, lactose monohydrate, or polyols. To accurately predict in vivo behavior, particle engineers must take hygroscopic growth into account in computational deposition models and in vitro cascade impactor characterization.

IV. INHALER DEVICE TECHNOLOGIES

A. Pressurized Metered-Dose Inhalers (pMDIs The pMDI, introduced in 1956 by Riker Laboratories (now 3M), remains the most widely prescribed inhaler globally. It consists of a drug formulation (solution or suspension) in a pressurized canister containing a liquefied propellant, a metering valve, and an actuator mouthpiece. Upon actuation, a precisely metered volume (typically 25–100 µL) is released through the valve, and the propellant flash-evaporates, atomizing the drug into an aerosol. The initial aerosol velocity is very high (~30–90 m/s), which, without a spacer, contributes to significant oropharyngeal deposition.

The 1989 Montreal Protocol mandated the global phase-out of chlorofluorocarbon (CFC) propellants (CFC-11, CFC-12, CFC-114) on grounds of ozone depletion. The pharmaceutical industry transitioned to hydrofluoroalkane (HFA) propellants—primarily HFA-134a (1,1,1,2-tetrafluoroethane) and HFA-227ea (heptafluoropropane)—which are ozone-neutral but carry global warming potentials (GWPs) of 1430 and 3220 times CO_2, respectively. Regulatory and environmental pressure is now driving a second propellant transition toward ultra-low GWP propellants. HFA-152a (GWP ~124) and HFO-1234ze(E) (GWP ~7) are currently in advanced pharmaceutical development. AstraZeneca and GSK have pledged carbon-neutral pMDI product lines by 2030.

Spacers and valved holding chambers (VHCs) attached to pMDIs decelerate and partially evaporate the aerosol plume, reducing oropharyngeal deposition from ~80% to <20% and improving pulmonary delivery efficiency to 35–55%. They are essential for pediatric patients, the elderly, and patients with poor inhalation technique.

B. Inhalers of dry powder (DPIs)

DPIs eliminate the need for propellants and the coordination requirement of pMDIs by harnessing the kinetic energy of the patient's inspiratory effort to disperse micronized medication powder into an inhalable aerosol. In order to optimize powder flow and metering, the drug is usually mixed with coarse lactose carrier particles (63–150 µm). When the medication is inhaled, aerodynamic forces separate the tiny drug particles from the carrier surfaces and carry them to the lung, while the larger carriers deposit in the oropharynx. Depending on the device and formulation, the fine particle fraction (FPF) that can be achieved with DPIs ranges from about 20% for passive, low-resistance devices to >50% for high-resistance devices in patients who can produce adequate inspiratory flow rates (≥60 L/min).

DPIs are divided into three categories based on the design of their powder reservoir: single-dose capsule inhalers (like HandiHaler and Breezhaler), multi-dose reservoir devices (like Turbuhaler and Genuair), and multi-dose blister strip inhalers (like Diskus and Ellipta). In order to eliminate inspiratory flow rate dependency, active DPIs—which use an internal energy source (battery-driven impeller, piezoelectric actuator, or compressed gas) to deagglomerate the powder independently of patient effort are being studied more and more. This is crucial for patients with severe COPD who have impaired respiratory muscle.

C. Nebulizers

Nebulizers are appropriate for patients who cannot use pMDIs or DPIs (infants, ICU-ventilated patients, severe acute exacerbations) because they transform liquid medication solutions or suspensions into fine aerosol mists for inhalation via tidal breathing. There are three primary kinds. Jet nebulizers are easy to use and reasonably priced, although they are inefficient (drug output ~30–40% of reservoir dose), produce wide particle size distributions, and take 10–20 minutes per treatment. They work by guiding pressurized gas, usually air or oxygen, through a liquid reservoir via a Venturi effect. In order to produce surface capillary waves that release aerosol droplets, ultrasonic nebulizers use a piezoelectric transducer vibrating at 1-3 MHz. These devices are quieter and faster, but they may denature thermolabile biologics because of cavitation heating.The state-of-the-art, vibrating mesh nebulizers (VMNs), create aerosols with narrow size distributions (MMAD 2–4 μm), high FPF (60–75%), minimal drug loss, and quick treatment times (5–10 minutes) at the expense of higher purchase prices and maintenance requirements. VMNs use a perforated mesh or plate with thousands of apertures (2–8 μm diameter) vibrated by a piezoelectric actuator.

D. SMIs, or soft mist inhalers

The only commercially approved device in this class, the Respimat® SMI (Boehringer Ingelheim), uses a special uniblock mechanism to create a slow-moving (~0.8 m/s vs ~30 m/s for pMDI), fine-droplet aerosol. A spring-driven piston pushes liquid drug solution through two convergent nozzles that impinge at an angle, creating a soft mist cloud that lasts for about 1.5 seconds. With lung deposition percentages of 50–65%, the slow velocity and tiny droplet size (MMAD ~1.5–3.5 μm) significantly minimize oropharyngeal deposition and are independent of patient inhaling effort. For COPD, SMIs (tiotropium, olodaterol, glycopyrronium/formoterol/budesonide combos) are authorized.

The following table comprehensively compares these inhaler modalities:

TABLE I. Comparative Analysis of Inhaler Device Technologies.

Device Type	MMAD (µm)	Fine Particle Fraction (%)	Coordination Needed	Suitable For
pMDI	1–5	15–30%	High	Asthma, COPD
pMDI + Spacer	1–3	35–55%	Low	Pediatrics, Elderly
DPI	2–5	20–50%	Moderate	Asthma, COPD, ILD
Nebulizer (Jet)	2–5	50–70%	None	Acute exacerbations
Mesh Nebulizer	2–4	60–75%	None	Cystic Fibrosis, ICU
Soft Mist Inhaler	1.5–3.5	50–65%	Low	COPD

Figure 3. Global Market Share by Inhaler Device Type (2024)

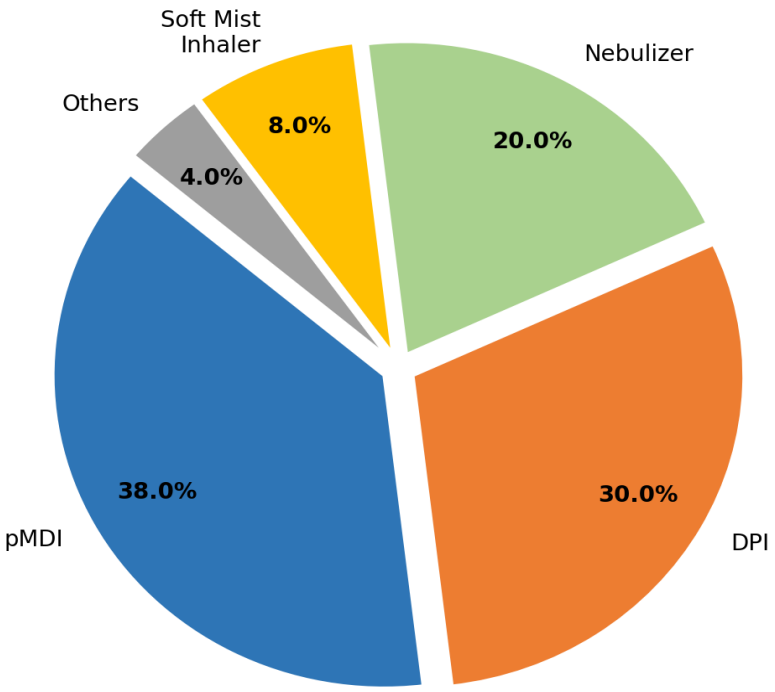

Fig. 3. Global inhaler device market share distribution (2024). pMDIs continue to dominate despite the environmental impact of HFA propellants. Source: GlobalData Pharma Intelligence, 2024.

V. MODERN FORMULATION METHODS FOR THE DELIVERY OF PULMONARY DRUGS

A. Traditional Formulations

Simple medication solutions or micronized drug crystals combined with grainy lactose made up the first inhaled formulations. Drug crystals with mass median geometric diameters (MMGDs) of 1–5 μm are produced by jet milling micronization; however, the high surface energy that results encourages aggregation, poor powder flow, and irregular dose emission. Superior particle engineering flexibility is provided by spray drying from aqueous or organic solvent solutions: spherical or wrinkled particles with controlled size, density, crystallinity, and surface composition can be produced by methodically varying process variables (inlet temperature, feed concentration, spray rate, and atomization air pressure).

B. Formulations of Liposomes:

Particle diameters of liposomes range from 50 nm for small unilamellar vesicles to several micrometers for gigantic unilamellar vesicles. Liposomes are spherical vesicles made up of one or more phospholipid bilayers encasing an aqueous core. Liposomes offer a number of therapeutic benefits for pulmonary delivery, including: (1) sustained drug release at the deposition site, extending the therapeutic effect while lowering peak plasma concentrations and systemic toxicity; (2) enhanced membrane permeability for hydrophilic drugs; (3) protection of encapsulated biologics (peptides, proteins, and nucleic acids) from enzymatic degradation; and (4) biocompatibility and biodegradability using naturally occurring phospholipids similar to components of pulmonary surfactants.

In 2018, the FDA approved Amikacin liposome inhalation suspension (ALIS; Arikayce®) for persons with refractory illness who had lung infections caused by Mycobacterium avium complex (MAC). There are several stages of clinical development for liposomal amphotericin B for pulmonary fungal prevention and liposomal cisplatin formulations for inhalation lung cancer treatment. Physical instability (aggregation, fusion, drug leakage), spray-drying liposomes to dry powder form, and reconstitution behavior are important formulation problems.

C. Nanoparticles made of polymers

Biodegradable polymers, including as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), chitosan, alginate, and poly(ε-caprolactone) (PCL), are used to create polymeric nanoparticles (PNPs) for pulmonary delivery. PLGA breaks down in vivo by random chain

scission hydrolysis into lactic and glycolic acid monomers that enter regular metabolic pathways. The FDA and EMA have approved PLGA for parenteral usage. Drug release profiles spanning days to months can be customized by changing the molecular weight and PLGA monomer ratio (75:25 vs. 50:50 LA:GA). In order to increase the paracellular transport of macromolecular medications, chitosan-based nanoparticles take advantage of the mucoadhesive qualities of chitosan, a cationic polysaccharide derived from crustacean chitin, to prolong residence time on mucosal surfaces and temporarily open tight junctions.

PNPs are usually spray-freeze-dried into redispersible powders or encapsulated within large porous particle (LPP) matrices for aerosol delivery. Surface functionalization with cell-penetrating peptides (CPPs), antibodies, or receptor ligands allows active targeting to particular lung cell populations, while PEGylation produces a hydrophilic brush layer that minimizes protein adsorption (opsonization) and decreases macrophage uptake.

D. Nanostructured Lipid Carriers and Solid Lipid Nanoparticles

With particle diameters ranging from 50 to 500 nm, solid lipid nanoparticles (SLNs) are colloidal systems made from solid lipids (glyceryl monostearate, tripalmitin, and cetyl palmitate) stabilized by phospholipids or surfactants. Within the lipid matrix, the drug is either molecularly distributed or in solid solution, allowing for prolonged release while the matrix gradually deteriorates. The second generation of lipid nanoparticles is known as nanostructured lipid carriers (NLCs), which incorporate liquid lipids into the solid lipid matrix to produce structural disorder that enhances drug loading capacity and stops drug expulsion during storage. Both platforms have been thoroughly studied for pulmonary administration of nucleic acids, antituberculosis medicines, and lipophilic anti-asthmatic medications (budesonide, beclomethasone).

E. Dendrimers

Dendrimers are hyperbranched, tree-like macromolecules with carefully regulated molecular weight, surface functional groups, and architecture. Polyamidoamine (PAMAM) dendrimers of generations 4 (G4) and 5 (G5), with diameters of about 4.5 and 5.4 nm, respectively, have been studied as pulmonary drug carriers. Through covalent conjugation or electrostatic contact, their large surface area-to-volume ratio allows for significant drug loading; terminal amine groups provide mucoadhesive and cell-penetrating qualities. To increase biocompatibility, surface modification techniques like PEGylation or acetylation are required since cationic PAMAM dendrimers show dose-dependent cytotoxicity.

F. New Biological Carriers: Extracellular Vesicles and Exosomes

Exosomes are extracellular vesicles (30–150 nm) produced from endosomes that cells normally secrete as a means of intercellular communication. Their natural membrane composition avoids immune surveillance, surface proteins facilitate cell-specific targeting, and their lipid bilayer structure allows loading of both hydrophilic (aqueous lumen) and lipophilic (bilayer) cargo, all of which make them appealing drug delivery vehicles. In mice with acute lung damage and pulmonary fibrosis, inhaled exosomes containing anti-inflammatory miRNAs have shown effective. The main obstacle to translation is the difficulty of producing scalable, consistently high-quality exosomes that adhere to Good Manufacturing Practice (GMP).

TABLE II. Advanced Pulmonary Drug Delivery Formulation Strategies: Comparison.

Formulation	Particle Size Range	Key Advantage	Limitation
Liposomes	100–400 nm	Sustained release; biocompatible	Stability issues
Polymeric Nanoparticles	100–500 nm	Controlled release; surface functionalization	Toxicity concerns
PLGA Microspheres	1–5 µm	Biodegradable; prolonged action	Complex manufacturing
Solid Lipid NPs	50–500 nm	High drug loading; stable	Low encapsulation efficiency
Dry Powder Particles	1–5 µm	No propellant; stable shelf life	Moisture sensitivity
Dendrimers	2–10 nm	High surface area; targeted delivery	High cost
Exosome-based	30–150 nm	Natural carrier; immune evasion	Yield scalability

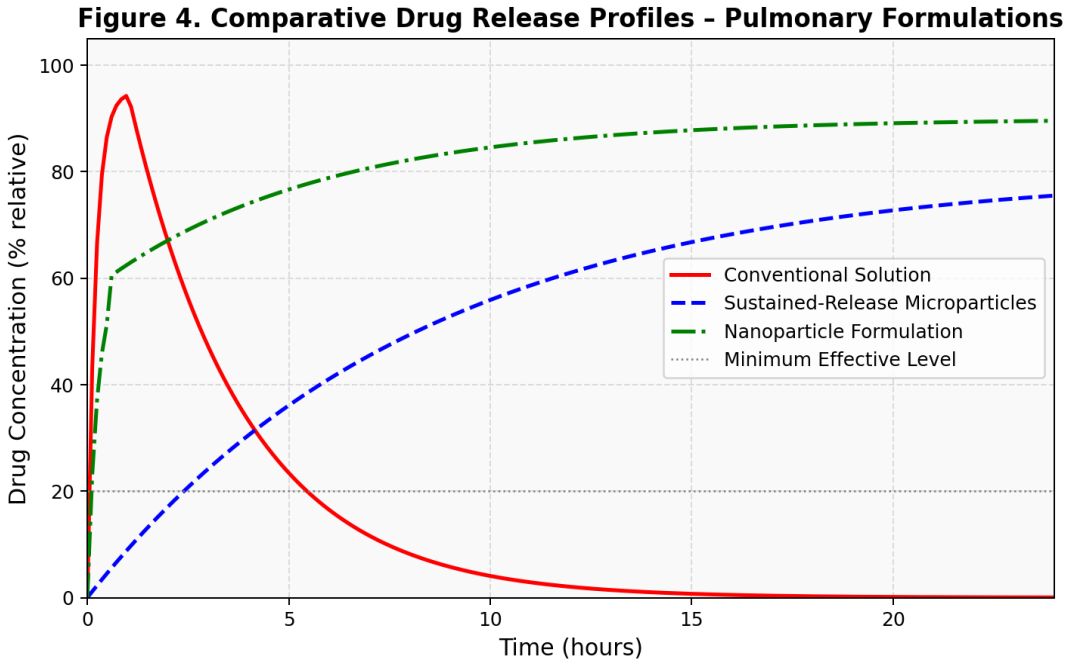

Fig. 4. Comparative drug release profiles for conventional solution, sustained-release microparticles, and nanoparticle formulations following pulmonary deposition. Nanoparticle formulations demonstrate biphasic release with an initial burst followed by sustained release above the minimum effective drug level.

VI. STIMULI-RESPONSIVE, TARGETED, AND SMART DELIVERY SYSTEMS

A.Strategies for Active Targeting

Particle size-dependent deposition patterns are essential for lung passive targeting. By adding molecular recognition components to the particle surface, active targeting activates particular receptors that are overexpressed on sick cells or pertinent immune populations. Folate-decorated PLGA nanoparticles loaded with rifampicin and isoniazid have been used to target folate receptor-β, which is overexpressed on activated alveolar macrophages in tuberculosis and inflammatory lung diseases. This has resulted in 10-fold higher intracellular drug concentrations in macrophage cell lines compared to non-targeted counterparts. While SP-B-mimetic lipopeptides conjugated to nanoparticles take use of the SP-B receptor on alveolar type II pneumocytes for preferential uptake and transcytosis, transferrin receptor-targeted nanoparticles have been used to target lung cancer cells.

B. Systems That Respond to pH

Drug release can be selectively triggered by taking advantage of the acidic milieu of tumor tissue (pH 6.5–6.8 vs. normal tissue pH 7.4) and the inflamed airway mucus (pH 5.5–6.5 in COPD). Poly(methacrylic acid) (PMAA), Eudragit® L100, and zwitterionic lipids are

examples of pH-sensitive polymers that are intact at physiological pH but undergo protonation-induced swelling or disintegration in acidic conditions, releasing encapsulated medication selectively at the disease site. By minimizing drug release in healthy tissue and increasing local concentration at the target, this approach improves the therapeutic index.C

C. Systems That Respond to Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS: superoxide, $H2O_2$, hypochlorite) are significantly enhanced in the airway microenvironment in COPD, asthma, and lung infections. In healthy tissue, nanoparticles carrying ROS-cleavable linkers—such as thioketal, aryl boronate, or selenium-containing bonds—remain intact, but they quickly break down in the oxidatively challenged disease microenvironment, allowing for on-demand drug release. In mouse models of LPS-induced acute lung injury, thioketal-linked nanoparticles loaded with siRNA targeting TNF-α have shown therapeutic efficacy with little systemic exposure.

D. Mucus-Penetrating and Thermo-Responsive Systems

The lower critical solution temperature (LCST) of thermoresponsive polymers based on poly(N-isopropylacrylamide) (PNIPAM) is about 32°C. Above this temperature, the polymers change from hydrophilic (swollen) to hydrophobic (collapsed) states. Thermoresponsive particles can be designed to release medication when they come into contact with the warm airway mucosa by adjusting the LCST to physiological airway temperature (37°C) through copolymerization. By minimizing interaction with mucin glycoproteins through dense PEG coating (surface density ≥0.2 PEG chains/nm^2), mucus-penetrating particles (MPPs) overcome the mucus barrier and enable rapid diffusion through mucus to the underlying epithelium. This strategy is especially crucial for drug delivery in hypersecretory conditions like cystic fibrosis and COPD.

E. Integration of Digital Health and Artificial Intelligence

One of the most revolutionary developments in inhaler technology is the combination of AI and digital health technologies with pulmonary medicine delivery. Real-time adherence and inhalation technique data are generated by smart inhalers with Bluetooth connectivity, dose counters, flow sensors, and GPS-based environmental monitoring (Propeller Health, Hailie sensor, Adherium Smartinhaler). This data is then sent to cloud platforms that are accessible by both patients and clinicians. Applying machine learning algorithms to this data allows for proactive dose escalation or physician consultation by predicting exacerbation risk two to five days ahead of time

By predicting regional drug deposition for various device-formulation combinations in a patient's airway anatomy, AI-powered digital twins of patient-specific airway geometries—derived from CT imaging and computational fluid dynamics (CFD) modeling—allow for personalized inhaler prescription. In simulated studies, this strategy has shown the potential to boost therapeutic efficiency by 30–45% when compared to population-average prescribing.

VII. PULMONARY DRUG DELIVERY'S CLINICAL APPLICATIONS

A. Asthma

Asthma is the primary indication for inhaled medications and affects about 300 million individuals worldwide (WHO, 2023). The development of the pMDI in the 1950s and the DPI in the 1970s made the cornerstone of asthma pharmacotherapy possible: short-acting β_2-agonists (SABAs) like salbutamol/albuterol for rescue and inhaled corticosteroids (ICS) like beclomethasone dipropionate, budesonide, and fluticasone propionate for maintenance. ICS/long-acting β_2-agonists (ICS/LABA, e.g., budesonide/formoterol, fluticasone/salmeterol) and increasingly ICS/LABA/long-acting muscarinic antagonists (LAMA, triple therapy) are administered via inhaler in modern combination therapy, which achieves better disease control with a lower systemic steroid burden than any oral formulation.

Biologic therapies targeting type 2 inflammatory pathways (anti-IgE, anti-IL-4Rα, anti-IL-5/IL-5Rα, anti-TSLP) are currently administered parenterally; however, extensive research is ongoing to reformulate these large molecular weight biologics for inhaled delivery using spray-dried powder or liposomal encapsulation strategies that protect protein integrity during aerosolization.

B. COPD, or chronic obstructive pulmonary disease

Inhaled bronchodilators are the main treatment for COPD, which affects around 251 million people worldwide and is expected to rank as the third most common cause of death by 2030. LABAs (formoterol, salmeterol, indacaterol, olodaterol, vilanterol) and long-acting muscarinic antagonists (LAMAs: tiotropium, umeclidinium, aclidinium, glycopyrronium) are available as DPIs, pMDIs, and SMIs for both monotherapy and combination therapy. In high-risk COPD patients, triple treatment (LAMA/LABA/ICS) administered in a single inhaler device (such as Trelegy Ellipta or Breztri Aerosphere) has been shown to significantly lower exacerbation rates and death.

C. Fibrosis Cystic

Mutations in the CFCE gene, which codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, cause cystic fibrosis (CF), which is characterized by thick, persistent mucus that obstructs airways and fosters the long-term colonization of bacteria, primarily Pseudomonas aeruginosa. (1) mucolytics (dornase alfa/Pulmozyme, a recombinant human DNase administered by VMN nebulizer, cleaves extracellular DNA in mucus to reduce viscosity); (2) osmotic agents (inhaled hypertonic saline 7%, mannitol DPI/Bronchitol) that hydrate the airway surface liquid; and (3) inhaled antibiotics (tobramycin inhalation solution/TOBI, aztreonam lysine/Cayston, and colistimethate sodium) to suppress chronic Pseudomonas infection. Although they are currently oral treatments, CFTR modulators (ivacaftor, tezacaftor, and elexacaftor) are potential targets for pulmonary reformulation.

D. PAH, or pulmonary arterial hypertension

Right heart failure and mortality are the results of PAH's gradual obliteration of the pulmonary vasculature. Because they quickly deactivate in the systemic circulation, inhaled prostanoids such as treprostinil (Tyvaso, ultrasonic nebulizer; Tyvaso DPI, Dreamboat device) and iloprost (Ventavis, jet nebulizer, 6–9 inhalations/day) provide focused pulmonary vasodilation with minimal systemic hypotension. The first and only inhaled dry powder prostanoid, Tyvaso DPI, was approved in 2022, greatly increasing treatment compliance and ease. These drugs have been shown in clinical trials to enhance 6-minute walk distance by 23–35 meters and lower pulmonary vascular resistance (PVR).

E. Infectious Lung Conditions

By delivering high local medication concentrations that surpass the minimum inhibitory concentration (MIC) for resistant microorganisms while minimizing systemic toxicity, the inhalation route presents strong benefits for treating pulmonary infections. At equivalent systemic doses, lung tissue concentrations of inhaled amikacin (ALIS, Arikayce®) are eight times greater than those of intravenous amikacin. Phase III trials have examined ciprofloxacin DPI (Linhaliq) for Pseudomonas infections linked to bronchiectasis. In Europe, inhaled colistimethate sodium (Colobreathe) is approved to treat Pseudomonas linked to cystic fibrosis. Through improved lung tissue penetration and macrophage-targeted administration, inhaled PLGA-encapsulated rifampicin, pyrazinamide, and isoniazid

formulations for tuberculosis are in pre-clinical and early clinical development and may reduce treatment duration.

F. Cancer of the Lung

The lung is a common metastatic target as well as the most common site of initial cancer (small cell lung cancer, SCLC; non-small cell lung cancer, NSCLC). The difficulty of obtaining sufficient tumor penetration in a consolidated or atelectatic region and the regulatory requirements for precise dosimetry have hampered inhaled chemotherapy, despite its conceptual attractiveness due to direct tumor access and avoidance of systemic toxicity. In rodent orthotopic lung cancer models, doxorubicin-loaded nanoparticles, paclitaxel microspheres, and inhaled cisplatin liposomes (LiPlaCis) have all shown tumor regression. Emerging research approaches include immunotherapy using inhaled checkpoint inhibitors and inhaled IL-2 for pulmonary metastases.

G. Lung-Based Systemic Drug Administration

The alveolar route is appealing for macromolecular treatments that cannot be taken orally because it offers quick absorption kinetics that are comparable to subcutaneous or intravenous injection for systemic drug delivery. The FDA approved inhaled insulin (Afrezza®, MannKind Corporation) for adults with type 1 and type 2 diabetes in 2014. It uses the Technosphere® dry powder platform (fumaryl diketopiperazine microparticles that release insulin upon alveolar contact with the aqueous hypophase) to achieve peak serum insulin concentrations within 12–15 minutes of inhalation (as opposed to 60–90 minutes for subcutaneous rapid-acting analogs). Erythropoietin for anemia, parathyroid hormone for osteoporosis, and interferon-β for multiple sclerosis are further systemic targets being studied.

TABLE III. Selected Clinical Trials and Approved Inhaled Therapeutics.

Drug/System	Disease	Trial Phase	Key Outcome
Inhaled Insulin (Afrezza)	Type 1 & 2 DM	Phase III / Approved	Comparable glycemic control; rapid onset (15 min)
Ciprofloxacin DPI	Bronchiectasis	Phase III	53% reduction in exacerbation frequency vs placebo
Inhaled Amphotericin B	Fungal prophylaxis	Phase II/III	86% reduction in invasive pulmonary aspergillosis
Treprostinil (Tyvaso)	PAH	Approved	Improved 6-minute walk distance by 23 m vs baseline

mRNA-LNP (COVID-19)	COVID-19 / Lung	Phase I/II	>90% lung bioavailability; systemic levels negligible
Nintedanib + Inhaler	IPF	Phase II	46% reduction in FVC decline compared to oral route

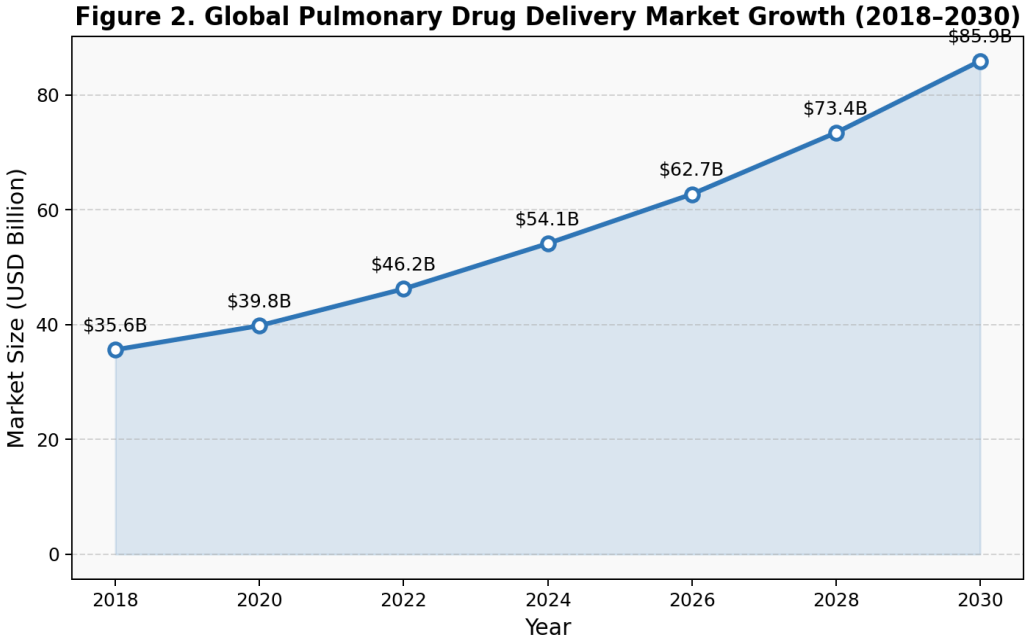

Fig. 2. Projected global pulmonary drug delivery market growth, 2018–2030 (USD Billion). Growth is driven by escalating COPD/asthma burden, novel biologic reformulations, and smart inhaler adoption. Source: Grand View Research, 2024; MarketsandMarkets, 2023.

VIII. DIFFICULTIES AND BARRIERS IN THE DELIVERY OF PULMONARY DRUGS

A. Clearance of Mucociliary

The main non-phagocytic defensive mechanism of the conducting airways is mucociliary clearance (MCC), which eliminates inhaled particles—including medication particles—from the tracheobronchial tree within a day of deposition. In healthy airways, the coordinated metachronal beating of cilia at about 15 Hz propels the gel-on-sol mucus bilayer, resulting in a mucus transport velocity of 4–20 mm/min. Particle surface chemistry, size, charge, and shape all affect the rate of mucociliary clearance of particles deposited in the conducting zone, which are mostly removed by MCC. MCC is compromised in conditions including CF, primary ciliary dyskinesia (PCD), and COPD, which paradoxically permits a longer medication residence duration while also leading to pathological mucus accumulation.

Developing mucus-penetrating nanoparticles (MPPs) that diffuse through the mucus gel layer more quickly than mucociliary transport; coadministering mucolytics to decrease mucus

viscoelasticity; focusing drug delivery on the alveolar zone, which lacks ciliated epithelium; and employing mucoadhesive polymers to reversibly bind particles to mucin glycoproteins and lower transport velocity are some strategies to get around MCC as a drug delivery barrier.

B. Phagocytosis of Alveolar Macrophages

Alveolar macrophages effectively remove particles larger than 0.5–1 μm that are deposited in the alveolar space, as explained in Section II. A key tension in PDDS design arises because the ideal aerodynamic size for alveolar deposition (1–3 μm) resides within the AM phagocytic sweet spot. Creating porous or elongated particles with a large geometric diameter but an appropriate aerodynamic diameter, surface PEGylation to reduce opsonin adsorption, and surface display of CD47 peptide mimetics that interact with SIRPα receptors on macrophages to deliver an inhibitory "don't eat me" signal are some of the particle engineering techniques used to lower AM clearance.

C. Chemical and Enzymatic Degradation

A variety of proteases (elastase, cathepsins, tryptase), nucleases, and oxidative enzymes found in the lung lining fluid can break down peptide, protein, and nucleic acid medications prior to absorption. Drug-metabolizing enzymes, such as CYP450 isoforms, which may biotransform inhaled medications, are also expressed by epithelial cells. Encapsulation within nanoparticulate carriers, the use of protease inhibitor excipients (such as aprotinin and soybean trypsin inhibitor), formulation as amorphous solid dispersions to prevent protein aggregation, and PEGylation to produce steric shields against enzymatic access are all ways to prevent biologics from degrading.

D. Patient-Related Elements

Studies consistently show that 50–70% of patients use their inhalers incorrectly, with the most frequent mistakes being failing to exhale before inhalation, insufficient inspiratory flow rate, inadequate breath-hold after inhalation, and failing to shake suspension-based pMDIs. Patient adherence to inhaled therapy is generally poor. In the United States alone, non-adherence to treatment for asthma and COPD is thought to be responsible for 300,000 avoidable hospital admissions each year, with related expenses surpassing $25 billion. In real-world trials, smart inhaler technologies that incorporate digital adherence tracking, electronic prescription integration, and embedded feedback mechanisms (visual or audio coaching) are showing notable gains in adherence.

E. Complexity of Manufacturing and Regulation

Regulations pertaining to inhaled medicinal products are particularly strict. Most jurisdictions regulate both the drug substance and the device as a combined product. Aerodynamic particle size distribution (APSD) measured by Next Generation Impactor (NGI) or Andersen Cascade Impactor (ACI) in accordance with all applicable pharmacopeial methodologies (USP <601>, Ph. Eur. 2.9.18), delivered dose uniformity, moisture content for DPIs, extractables/leachables from device components, and in vitro–in vivo correlation (IVIVC) are examples of critical quality attributes (CQAs). A complicated array of pharmacokinetic, pharmacodynamic, and in vitro tests are necessary to demonstrate bioequivalence for generic inhaled medications; this regulatory burden severely restricts the market entry of generic inhalers and keeps drug costs high.

F. Sustainability of the Environment

The combined CO2-equivalent footprint of HFA propellants in pMDIs is projected to be between 10 and 37 million metric tons per year, or around 4% of the overall carbon footprint of the NHS (U.K.). Key elements of pharmaceutical industry sustainability plans include switching to low-GWP propellants (HFA-152a, HFO-1234ze), increasing the usage of DPIs (which have around a 20-fold smaller carbon footprint per dosage than HFA pMDIs), and recycling programs for aluminum canisters. To encourage the switch to low-GWP inhalers while maintaining clinical equivalency, regulatory bodies in the US and Europe are creating policy frameworks.

IX. IN VITRO CHARACTERIZATION TECHNIQUES FOR FORMULATIONS INHALED

The foundation of inhaled product development is thorough in vitro characterization, which offers proxy measurements of in vivo performance that direct formulation modification and regulatory dossier preparation. The following are the main techniques included in the pharmacopeial testing battery for inhaled goods..

By sorting aerosol particles into successive impaction stages of diminishing aerodynamic cut-off diameter, cascade impaction utilizing the Andersen Cascade Impactor (ACI) or Next Generation Impactor (NGI) determines the APSD. A validated HPLC-UV or HPLC-MS test is used to quantify the drug mass collected at each stage, producing MMAD, GSD, fine particle fraction (FPF), and fine particle dose (FPD). Dissolution rate data that correlates with pulmonary absorption kinetics is obtained through in vitro dissolution tests in simulated lung

fluids (SLF) modeled on human epithelial lining fluid composition (Franz cells, USP dissolution equipment). A more straightforward two-stage method for FPF quality control for DPIs is twin impinger (TI) testing. Without the need for stage collection, laser diffraction analysis (SYMPATEC HELOS, Malvern Spraytec) offers quick, continuous aerosol sizing. It is mainly useful for nebulizers.

Ex vivo lung models that replicate airway bifurcations, mucus secretion, and surfactant dynamics using excised pig or ovine lungs placed in ventilated chambers offer a more physiologically accurate deposition assessment than cascade impactors. The cutting edge of biorelevant in vitro testing is represented by airway-on-chip microfluidic platforms that use primary human bronchial epithelial cells differentiated at the air–liquid interface (ALI). These platforms allow for the simultaneous measurement of aerosol deposition, mucociliary transport, transepithelial electrical resistance (TEER), and drug absorption kinetics in a single integrated experiment.

X. FRAMEWORKS OF REGULATION FOR INHALED DRUG PRODUCTS

The Office of Pharmaceutical Quality (OPQ) and Division of Pulmonology, Allergy, and Rheumatology Products (DPARP) at the U.S. FDA, the Respiratory and Allergy Products working party at the European Medicines Agency (EMA), the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom, and similar organizations in Japan (PMDA), China (NMPA), and India (CDSCO) are responsible for regulatory oversight of inhaled drug-device combination products. The regulatory framework recognizes that modifications to the formulation or device component may modify the delivered dose and aerosol properties, and it addresses the inseparable drug-device interaction inherent to inhaled goods.

Pharmaceutical quality standards, such as given dosage uniformity testing throughout the device's useable life, priming and repriming studies, the impact of storage orientation, and use at temperature and humidity extremes, are outlined in the FDA's 2018 guidance on MDIs and DPIs. A tiered approach is used to evaluate the bioequivalency of generic inhaled products: in vitro aerodynamic characterization, pharmacokinetic studies (plasma PK for systemically absorbed drugs), pharmacodynamic studies (FEV_1 for bronchodilators), and clinical end-point studies if the in vitro/PK data is not sufficient.

TABLE IV. Key Regulatory Guidance Documents for Inhaled Drug Products.

Guideline	Issuing Body	Year	Key Requirement
MDI / DPI Guidance	U.S. FDA	2018 (rev.)	In-vitro / in-vivo correlation; dose uniformity
EMA/CHMP/QWP	EMA	2006 (rev. 2022)	Aerodynamic particle size distribution testing
ISO 27427:2022	ISO	2022	Nebulizing systems performance standards
ICH Q6A	ICH	1999 (applicable)	Specifications for drug substances/products
USP <601>	USP	Current	Inhalation and nasal drug products standards

XI. NEW FRONTIERS AND FUTURE DIRECTIONS

A. RNA-Based Pulmonary Treatments and Gene Therapy

Given that breathed vectors can reach the airway epithelium, the respiratory system is a desirable target for gene therapy. The main delivery technologies include non-viral lipid nanoparticle (LNP) systems and viral vectors, especially adeno-associated virus (AAV) serotypes AAV2, AAV5, and AAV9, which have different tropism for airway and alveolar cells. Phase I/II clinical studies for inhaled AAV-mediated gene therapy for cystic fibrosis (CF) are underway, and preliminary results indicate sustained restoration of CFTR function in airway epithelial cells. Inhaled mRNA-LNP formulations, validated by the success of COVID-19 mRNA vaccines, are now being investigated for CFTR mRNA replacement (for CF patients with rare mutations not addressed by current modulators), surfactant protein B (SP-B) deficiency, and alpha-1 antitrypsin (A1AT) deficiency In preclinical models, siRNA-based inhaled treatments that target SARS-CoV-2 RNA, RSV nucleoprotein, and inflammatory mediators (TNF-α, IL-6, and IL-8) in ARDS have shown promising efficacy. The two main obstacles to siRNA inhalation are their requirement for endosomal escape after cellular uptake and their vulnerability to nuclease destruction in airway lining fluid; both issues are addressed by LNP formulations that include ionizable lipids.

B. Mucosal Immunity and Inhaled Vaccines

Systemic injection cannot effectively generate secretory IgA-mediated immunity at the primary site of pathogen entry for respiratory viruses, whereas mucosal vaccination through the respiratory route may. Clinical trials have assessed inhaled whole-inactivated influenza, measles, and TB (BCG) vaccinations; the measles aerosol vaccine showed non-inferior

seroconversion rates when compared to subcutaneous injection. Research into inhaled mRNA and viral-vectored vaccines (inhalation ChAdOx1 nCoV-19, inhaled BNT162b2 LNP reformulations) was accelerated by the COVID-19 pandemic; as of 2024, several candidates were in Phase I/II studies. Inhaled vaccinations have been designated as a strategic priority for the upcoming pandemic preparation framework by the Mucosal Vaccine Consortium (MVC) and CEPI.

C. Customized and Accurate Pulmonary Care

Personalized inhaler prescriptions based on anticipated individual deposition efficiency are made possible by the combination of verified CFD deposition models and patient-specific airway geometry reconstructed from HRCT imaging. High-resolution resin printing has made it possible to 3D print patient-specific airway replicas for device testing and optimization. By identifying genetic variants in β_2-adrenoceptor (ADRB2 Arg16Gly, Gln27Glu), FKBP5, and IL4RA genes that affect drug response, pharmacogenomic profiling of patients allows for genotype-guided selection of inhaled corticosteroid dose, bronchodilator class, and biologic therapy, advancing the field of precision medicine in respiratory disease.

D. Bioinspired Device Design and 4D Printing

The creation of inhalers with geometrically complicated flow channels optimized by computational design for optimal aerosol deagglomeration efficiency at particular inspiratory flow rates is made possible by developments in additive manufacturing (3D and 4D printing). A route to true patient-adaptive DPIs is provided by shape memory polymer actuators that automatically modify device resistance in response to patient-generated flow. Innovative methods for passive powder deaggregation are being offered by bioinspired device designs that imitate the morphology of natural aerosol dispersers (pollen release mechanisms, fungal spore dispersal)

XII. SUGGESTED RESEARCHER PRIOR LITERATURE

The foundational reading list for every researcher working in this topic consists of the following seminal works. They cover everything from clinical pharmacology to aerosol physics and are arranged thematically.

A. Modeling Lung Deposition and Aerosol Physics

The standard reference for human respiratory tract dosimetry models is still ICRP Publication 66 (1994). The fundamental mathematical treatment of aerosol formation, transport, and deposition can be found in Finlay's textbook "The Mechanics of Inhaled Pharmaceutical Aerosols" (Academic Press, 2001). An updated review of particle deposition in lung models

is given by Darquenne (2012, J Aerosol Med). CFD validation standards for in silico deposition prediction were developed by Longest & Holbrook (2012, J Aerosol Sci)

B. Technology of Inhaler Devices

The formulation and performance of pMDI were thoroughly examined by Newman (2004, Respir Med). The criteria for evaluating DPI performance were established in the consensus study by Crompton et al. (2006, Respir Med). Real-world efficacy across device classes was compared by Price et al. (2013, Int J COPD). Inspiratory flow rate and DPI performance were measured by Haidl et al. (2016, Respir Med). The seminal review of aerosol medication delivery to the lungs was published in Dolovich & Dhand (2011, Lancet)

C. Particle engineering and formulation

The big porous particle idea, which revolutionized DPI formulation science, was first presented by Edwards et al. (1997, Science). The comprehensive overview of inhaling medications was given by Patton & Byron (2007, Nat Rev Drug Discov). Vehring (2008, Pharm Res) examined spray drying for inhalation particle engineering in a methodical manner. Hadinoto et al. (2013, Int J Pharm) examined pulmonary medication delivery by nanoparticles. The crucial importance of particle shape in phagocytic uptake was shown by Champion & Mitragotri (2006, PNAS).

D. Liposomal Systems and Nanoparticles

Lipid nanoparticles as medication carriers were first reviewed by Torchilin (2005, Nat Rev medication Discov). A review of liposomal formulations for pulmonary administration was conducted by Seville et al. (2007, Drug Deliv). Biodegradable polymeric nanoparticles for pulmonary applications were examined by Rytting et al. (2008, Expert Opin Drug Deliv). Mansour et al. (2009, Int J Pharm) investigated liposomes as a pulmonary medication delivery method.

E. Digital Health and Smart Inhalers

Sulaiman et al. (2019, Respir Med) showed that Bluetooth-enabled inhalers improved real-world adherence. Electronic inhaler adherence tracking was examined by van der Palen et al. (2016, ERJ Open Res). The CRITIKAL study comparing inhaler technique and asthma outcomes was published by Foster et al. (2017, J Allergy Clin Immunol).

XIII. CONCLUSION

From a straightforward empirical practice, pulmonary medication administration has developed into a complex, multidisciplinary discipline that incorporates digital technology, aerosol physics, polymer chemistry, device engineering, and clinical pharmacology. The

respiratory route is an essential route for both local lung disease management and systemic medication delivery because of its distinct anatomical and physiological features, which include its large surface area, thin air–blood barrier, rich vasculature, and direct access to pulmonary pathologies.

This review has shown that there isn't a single tool, formula, or approach that works for everyone. Instead, a comprehensive, patient-centered design approach that incorporates particle engineering (size, density, shape, surface chemistry), device mechanics (resistance, emitted dose, plume characteristics), formulation science (carrier selection, drug-polymer interaction, release kinetics), and clinical pharmacology (target site, disease pathophysiology, patient population) is necessary for optimal pulmonary drug delivery. The development of biological therapeutics (mRNA, gene vectors, exosomes), intelligent materials (stimuli-responsive nanoparticles), and digital health tools (smart inhalers, AI-guided prescribing) is expected to extend the therapeutic reach of inhaled medication into previously unreachable areas

.Closing the gap between in vitro predictability and in vivo performance, overcoming the biological obstacles of mucociliary clearance and macrophage phagocytosis for macromolecular payloads, addressing propellant sustainability without sacrificing clinical efficacy, enhancing patient adherence and inhaler technique through education and digital feedback, and navigating the intricate regulatory pathway for novel drug-device combination products are some of the main challenges that lie ahead. It will need unprecedented cooperation between academic institutions, business, government agencies, and patient advocacy groups to address these issues.

Innovation in pulmonary drug administration is more important than ever due to the rising burden of respiratory diseases, which is exacerbated by air pollution, antibiotic resistance, viral pandemics, and aging populations worldwide. The discipline is at a pivotal point where a new age of targeted, customized, and efficient inhalation therapies is promised by the intersection of nanotechnology, genetics, artificial intelligence, and materials science.

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