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REVIEW ARTICLE

A Review on Pathogenesis and Advances in Pulmonary Drug Delivery for Chronic Obstructive Pulmonary Disease

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Abstract: Chronic obstructive pulmonary disease is a persistent, debilitating respiratory disorder characterized by progressive airflow limitation, chronic bronchial inflammation, and parenchymal tissue destruction. Environmental insults, primarily chronic cigarette smoke exposure and airborne particulate matter, trigger an amplified inflammatory cascade governed by alveolar macrophages, neutrophils, and cytotoxic T-lymphocytes. This pathological sequence drives proteolytic tissue breakdown, peripheral airway remodeling, and excessive mucociliary dysfunction. While standard pharmacological regimens rely on bronchodilator and anti-inflammatory regimens to alleviate bronchospasm, conventional systemic interventions remain constrained by poor bioavailability, rapid enzymatic clearance, and systemic adverse reactions. Targeted inhalation therapy directly overcomes these anatomical and physiological limitations by delivering active therapeutic molecules straight to the terminal bronchial tree and alveolar surfaces, circumventing hepatic first-pass metabolism while achieving elevated local drug concentrations. Inhalational drug delivery includes pressurized metered-dose inhalers, dry powder inhalers, and modern soft mist or vibrating mesh nebulizers, each displaying distinct fluid mechanical and dispersion characteristics. Similarly, formulations have evolved to address respiratory clearing mechanisms through engineered micro- and nanocarriers, including large porous microparticles, polymeric nanoparticles, liposomal suspensions, and stimuli-responsive platforms. Incorporating particle aerodynamics and patient-centric device optimization provides a valuable strategy to enhance deep lung deposition, mitigate oropharyngeal impaction, and improve therapeutic compliance across variable disease phenotypes.

Keywords: Chronic Obstructive Pulmonary Disease; Inhalation Device Technology; Pulmonary Drug Delivery; Aerodynamic Particle Sizing; Targeted Aerosols.

1. Introduction

Targeting the respiratory tract for localized and systemic drug administration possesses an extensive clinical advantage [1]. The human pulmonary system offers a distinct site for pharmacological absorption, characterized by an expansive surface area reaching approximately 100 to 140 m^2, an extremely thin alveolar-capillary endothelial boundary measuring 0.1 to 0.2 μm, and an abundant pulmonary microvascular perfusion network [2, 3]. In contrast to conventional oral and parenteral routes, localized pulmonary drug administration delivers pharmacologically active molecules directly to target receptors situated along the tracheobronchial tree and alveolar airspaces [4]. Consequently, lower nominal doses can elicit equivalent or superior local therapeutic efficacy while limiting systemic drug exposure, reducing unwanted peripheral off-target effects, and entirely bypassing hepatic first-pass enzymatic clearance [5].

Over recent decades, pulmonary delivery has evolved from an empirical administration route into a quantitatively engineered platform [6]. Historically, inhalational interventions focused largely on basic bronchodilatory or antimicrobial interventions, beginning with nebulized adrenaline in the 1920s, experimental pulmonary insulin delivery in 1925, and early inhaled penicillins in the 1940s. The inception of pressurized metered-dose inhalers (pMDIs) in 1956 established standardized, portable dosing for obstructive airway diseases [7]. Current inhalational pharmacology addresses complex macromolecules, therapeutic proteins, peptide fractions, synthetic gene-silencing vectors, and advanced small molecules designed for respiratory and systemic interventions [8, 9].

The therapeutic efficacy of an inhaled aerosol relies upon its physiological and mechanical deposition within designated anatomical compartments [10]. The upper conducting airways, which possess continuous pseudostratified columnar ciliated epithelia and a protective mucus blanket, act as an efficient physical barrier that eliminates inhaled foreign particles via mucociliary clearance. In contrast, the deeper non-ciliated alveolar region facilitates rapid solute uptake via passive transcellular diffusion, vesicular transcytosis, or paracellular channels [11]. Engineering inhalable formulations capable of penetrating beyond peripheral airway blockages remains critical in the therapy of obstructive respiratory pathologies [12].

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2. Pulmonary Drug Delivery

Aerosolized pharmaceutical administration dates back more than four millennia to ancient healing systems [13]. In Ayurvedic medical traditions, individuals suffering from respiratory distress inhaled smoke from burning leaves of *Datura stramonium*, leveraging anticholinergic tropane alkaloids to induce smooth muscle relaxation. Ancient Egyptian medical papyri documented the inhalation of vapors generated by placing *Hyoscyamus muticus* upon heated stones [14]. Early Persian physicians, notably Avicenna, documented inhalational applications using volatile resins, eucalyptus, and pine distillates to manage bronchial afflictions.

The Industrial Revolution accelerated mechanistic advancements in aerosol generation, initiating a transition from unmetered herbal smoke toward calibrated pharmaceutical suspensions [15]. The nineteenth century introduced early glass bulb atomizers and steam-driven nebulizers, allowing controlled aqueous phase delivery. During the mid-twentieth century, the pharmaceutical sector transformed device design through propellant-driven aerosolization, giving rise to chlorofluorocarbon (CFC)-based metered-dose systems [16]. Subsequent international treaties addressing environmental ozone depletion accelerated the transition to modern hydrofluoroalkane (HFA) propellants, engineered breath-actuated mechanisms, dry powder dispersion engines, and vibrating mesh liquid generation systems [17].

3. Pathophysiology of Chronic Obstructive Pulmonary Disease

3.1. Respiratory System and Alveolar Gas Exchange

Under normal physiological parameters, the human respiratory system maintains efficient gas exchange through a branching architecture of conducting airways terminating in approximately 300 to 500 million alveoli [18]. Ambient air traverses the nasopharynx, larynx, trachea, and sixteen to twenty-three generations of bifurcating bronchi and bronchioles to access functional alveolar airspaces [19]. Within these thin-walled units, oxygen readily diffuses across the alveolar epithelial barrier, traversing the pulmonary interstitial space and capillary endothelium to bind erythrocyte hemoglobin, while metabolically produced carbon dioxide is cleared down its concentration gradient during exhalation [20]. Healthy alveolar airspaces retain structural elasticity, expanding passively upon inspiration and recoiling via intrinsic elastic tensions during expiration. In chronic obstructive pulmonary disease (COPD), repeated exposure to noxious airborne particles impairs these homeostatic mechanics [21]. Chronic cellular inflammation alters the tissue balance toward persistent proteolysis, collagen destruction, small airway occlusion, and architectural deformation [22]. The structural disruption follows two principal pathological presentations that frequently co-exist within patients: pulmonary emphysema and chronic obstructive bronchitis.

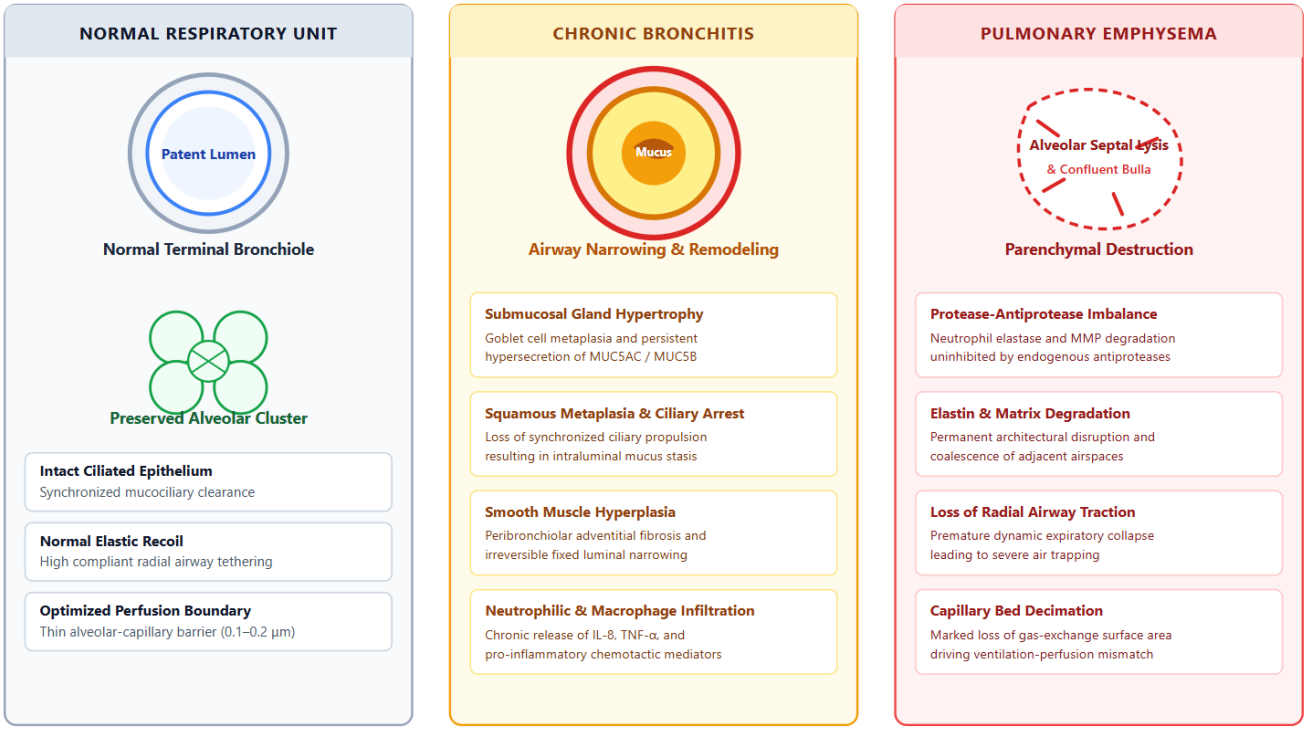

Figure 1. Pathophysiology of Chronic Obstructive Pulmonary Disease

3.2. Chronic Bronchitis and Luminal Remodeling

Chronic bronchitis is clinically categorized by a persistent, productive cough occurring for at least three consecutive months across two successive years in the absence of alternative respiratory etiologies [23]. Pathologically, prolonged exposure to xenobiotic irritants activates surface epithelial cells and subepithelial fibroblasts, resulting in goblet cell hyperplasia, submucosal glandular enlargement, and hypersecretion of thick mucin polymers, principally MUC5AC and MUC5B [24]. Concomitantly, the coordinated ciliary beat frequency declines, severely disrupting mucociliary transit. The accumulation of viscous secretions, combined with peribronchiolar fibrosis and intense inflammatory wall edema, narrows the small conducting airways, generating turbulent luminal resistance and dynamic expiratory airflow limitation [25].

3.3. Emphysematous Parenchymal Destruction

Emphysema is anatomically defined by permanent, abnormal enlargement of the airspaces distal to the terminal bronchioles, accompanied by destructive remodeling of the alveolar walls without marked mechanical fibrosis [26]. This condition involves an enzymatic imbalance between endogenous proteases, such as matrix metalloproteinases and neutrophil elastase, and antiprotease shields, primarily alpha-1 antitrypsin [27]. The degradation of elastin fibers compromises the structural framework of the alveolar walls, diminishing capillary perfusion surfaces and disrupting radial traction on intra-acinar airways [28]. During expiration, the absence of structural elastic recoil results in premature airway collapse, chronic air trapping, lung hyperinflation, and impaired gas diffusion, causing progressive hypoxemia and hypercapnia.

3.4. Diagnosis and Staging

Clinical grading of COPD severity is structured according to the functional classifications formulated by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [29]. The physiological criterion requires spirometric verification of an airflow limitation refractory to bronchodilator reversal, formally marked by a post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) below 0.70 [30].

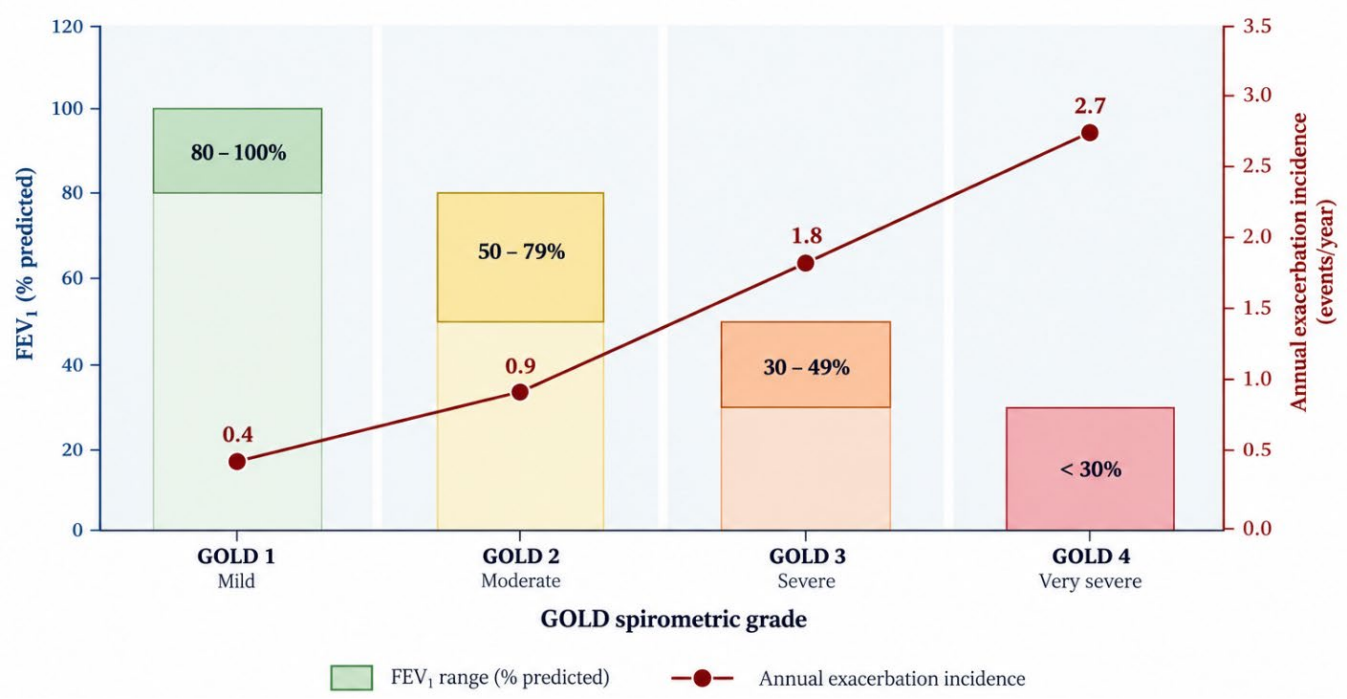

Figure 2. Stages of COPD (GOLD Classifications)

Once this post-bronchodilator threshold is identified, disease severity is graded across four functional stages based on percentage-predicted FEV_1 values:

3.4.1. GOLD Stage 1 (Mild)

Post-bronchodilator $FEV_1 \geq 80\%$ predicted normal value. Individuals typically show minimal exertional dyspnea, accompanied occasionally by a chronic dry or phlegmatic cough [31].

3.4.2. GOLD Stage 2 (Moderate)

50%≤FEV_1<80%predicted normal value. Airway resistance becomes pronounced during exertion, accompanied by chronic productive sputum, frequently prompting the initial medical consultation [32].

3.4.3. GOLD Stage 3 (Severe)

30%≤FEV_1<50%predicted normal value. Severe dyspnea during routine movements, diminished physical endurance, systemic cachexia, and recurring exacerbations that accelerate functional deterioration [33].

3.4.4. GOLD Stage 4 (Very Severe)

FEV_1<30%predicted normal value, or FEV_1<50%associated with persistent respiratory failure or signs of cor pulmonale [34]. At this stage, alveolar capillary gas exchange is severely compromised, presenting life-threatening risks during infectious decompensation.

Complementing spirometric stratification, modern clinical models integrate composite symptom scores, including the Modified Medical Research Council dyspnea index and the COPD Assessment Test, paired with annual historical counts of moderate-to-severe exacerbations, guiding pharmacological regimens across distinct patient risk phenotypes [35].

3.5 Etiological Drivers and Clinical Manifestations

Cigarette combustion emissions are the principal etiological driver of COPD globally, containing thousands of distinct chemical compounds, free radicals, and toxic gases [36]. Prolonged inhalation of combustible biomass fuels, environmental smog, workplace mineral dusts, and passive exposure to sidestream smoke generate additive inflammatory injuries [37]. A well-characterized genetic mechanism is severe hereditary alpha-1 antitrypsin deficiency, driven by mutations in the *SERPINA1* gene, which leaves the alveolar architecture vulnerable to uninhibited elastase digestion and drives early panacinar emphysema even in non-smoking individuals [38].

Clinically, COPD manifests as progressive exertional dyspnea, persistent cough, copious sputum production, audible chest wheezing, and recurring lower respiratory tract infections [39]. As the disease advances systemically, sustained systemic inflammation, oxidative stress, and hypoxia induce skeletal muscle wasting, nutritional cachexia, peripheral edema secondary to pulmonary arterial hypertension, and fatigue [40].

4. Therapeutic Management of COPD

4.1. Pharmacological Interventions

Pharmacological therapies aim to relieve dynamic airflow obstruction, reduce symptom burdens, diminish the frequency of acute exacerbations, and preserve remaining functional capacity [41]. Inhaled bronchodilators serve as fundamental maintenance drugs and are broadly divided into short-acting and long-acting classes:

4.1.1. Short-Acting Bronchodilators

Short-acting β_2-agonists, such as salbutamol and terbutaline, along with short-acting muscarinic antagonists, like ipratropium bromide, provide rapid relief of acute bronchospastic symptoms [42].

4.1.2. Long-Acting Bronchodilators

Long-acting β_2-agonists, including formoterol, salmeterol, and indacaterol, combined with long-acting muscarinic antagonists, such as tiotropium bromide, umeclidinium, and glycopyrronium, sustain airway patency over 12 to 24-hour intervals, improving static and dynamic lung compliance [43].

4.1.3. Inhaled Corticosteroids (ICS)

Agents such as fluticasone propionate, budesonide, and beclomethasone dipropionate are combined with long-acting bronchodilators for patients exhibiting frequent exacerbations, persistent airway hyperresponsiveness, or high systemic blood eosinophil counts [44].

4.1.4. Phosphodiesterase-4 Inhibitors

Oral roflumilast addresses intracellular cyclic adenosine monophosphate degradation within inflammatory cells, dampening neutrophil infiltration in chronic bronchitic phenotypes prone to frequent exacerbations [45].

4.2. Non-Pharmacological Interventions and Clinical Procedures

Supportive clinical approaches substantially influence long-term COPD prognosis. Smoking cessation remains the single most effective intervention to halt accelerated FEV_1 decline [46]. Annual administration of seasonal influenza vaccines, along with conjugated and polysaccharide pneumococcal vaccines, reduces the frequency of life-threatening respiratory infections and hospital admissions [47]. In individuals suffering from resting hypoxemic respiratory failure, defined by an arterial partial pressure of oxygen equal to or below 55 mmHg or oxygen saturation equal to or below 88%, long-term oxygen therapy administered for more than 15 hours daily preserves vital organ function, reduces pulmonary hypertension, and improves survival [48].

Pulmonary rehabilitation delivers a structured program that incorporates physical conditioning, respiratory muscle training, nutritional support, and disease self-management [49]. In individuals with severe emphysematous hyperinflation refractory to conservative regimens, surgical or bronchoscopic lung volume reduction can eliminate non-functional, hyperinflated lung areas [50]. In terminal cases meeting strict clinical criteria, bilateral orthotopic lung transplantation serves as an end-stage therapeutic option [51].

4.3. Botanical Extracts and Experimental Adjuncts

Certain bioactive botanical mixtures have been evaluated as supportive therapies for chronic respiratory inflammation [52]. The Anti-asthma Herbal Medicine Intervention, designated as ASHMI and composed of extracts from *Ganoderma lucidum*, *Sophora flavescens*, and *Glycyrrhiza uralensis*, has been assessed in both laboratory models and clinical trials [53].

Preclinical investigations show that active fractions from *Glycyrrhiza uralensis* downregulate inflammatory pathways, decreasing the release of interleukin-8, eotaxin-1, tumor necrosis factor-alpha, and nuclear factor kappa-B [54]. In murine models, the herbal formulation reduced allergen-provoked airway hyperresponsiveness, enhanced prostacyclin release, and limited mucosal hypersecretion [55]. Controlled clinical trials contrasting oral botanical formulations with standard glucocorticoids observed improvements in airflow and symptom scores, although systemic corticosteroid therapy retained superior efficacy across primary spirometric endpoints [56].

5. Biophysical Mechanism of Pulmonary Aerosol Delivery

5.1 Cellular Barriers of the Respiratory Epithelium

Inhaled therapeutic molecules must overcome a continuous series of physical and enzymatic barriers before reaching target receptors [57]. The conducting airways, spanning generations 0 through 16, are lined by a pseudostratified ciliated columnar epithelium covered with an aqueous periciliary fluid layer measuring roughly 7 μm in depth and an overlying gel-like mucus layer [58]. This continuous mucus matrix traps inhaled foreign particles, which are then cleared toward the oropharynx by coordinated ciliary beating. In chronic inflammatory diseases, goblet cell hyperplasia expands this barrier, impairing drug dispersion [59].

Once aerosols penetrate past the terminal bronchioles into the respiratory bronchioles and alveolar clusters across generations 17 through 23, they encounter the alveolar epithelium. This interface covers more than 95% of the alveolar surface via ultra-thin Type I alveolar pneumocytes measuring 0.1 to 0.2 μm in thickness, along with cuboidal Type II alveolar pneumocytes responsible for synthesizing endogenous pulmonary surfactant [60]. Intercellular tight junctions severely limit passive paracellular penetration of large hydrophilic macromolecules across this membrane [61]. Particulates that deposit along the alveolar surface are exposed to resident alveolar macrophages, which recognize and clear microparticles spanning 1.5 to 3.0 μm in diameter within hours of deposition [62].

5.2 Mechanisms of Solute Uptake

Molecules that avoid early macrophage clearance enter the systemic or interstitial spaces via distinct absorption routes [63]:

5.1.1. Transcellular Passive Diffusion

Lipophilic small-molecule drugs rapidly traverse the lipid bilayers of Type I alveolar cells along their concentration gradients, gaining immediate access to the pulmonary capillary bed.

5.1.2. Paracellular Transport

Small hydrophilic molecules displaying hydrodynamic radii below 1 nm traverse the intercellular aqueous pores regulated by tight junctions [64].

5.1.3. Receptor-Mediated Transcytosis and Fluid-Phase Vesicular Uptake

Peptides and large intact proteins undergo internalization through invaginating caveolae and endocytic vesicles, crossing the epithelial cytoplasm to undergo exocytic release into the interstitial basement membrane without disrupting membrane integrity [65].

5.3 Aerosol Aerodynamics and Deposition Kinetics

The regional deposition of inhaled pharmaceuticals depends on their aerodynamic behavior within the inspiratory air stream [66]. The primary determinant is the mass median aerodynamic diameter ($MMAD$), defined as the diameter of a sphere of unit density (1 g/cm^3) that possesses the identical settling velocity in air as the particle under examination [67]. Three physical principles govern aerosol deposition within the pulmonary tree:

5.1.4. Inertial Impaction

Occurs when particles have an $MMAD$ greater than 5 μm and high linear velocities. Unable to follow changing gas streamlines at tracheobronchial bifurcations, these larger particles collide with the mucous lining of the upper oropharynx, larynx, and primary bronchi, frequently leading to localized adverse reactions such as oral candidiasis and dysphonia [68].

5.1.5. Gravitational Sedimentation

Affects particles possessing an $MMAD$ between 1 and 5 μm traveling within the peripheral bronchioles and acinar regions where airflow rates decline significantly. Given sufficient breath-holding residence times of 5 to 10 seconds, these particles settle out of suspension under gravitational pull and deposit directly upon the ciliated and alveolar epithelia [69].

5.1.6. Brownian Diffusion

Governs sub-micron particulates with an $MMAD$ below 0.5 μm and nanoparticles within the terminal alveoli. Constant collisions with ambient gas molecules drive random displacement, facilitating contact with the alveolar wall; however, an estimated 50% to 80% of unengineered particles within this size range fail to deposit and are expelled during routine exhalation [70].

6. Inhalation Dosage Forms

Selecting an inhaler platform relies on balancing device physics against individual patient physiological capabilities [71]. Modern inhalation systems encompass pressurized metered-dose inhalers, dry powder inhalers, soft mist inhalers, and specialized nebulizers [72].

6.1. Pressurized Metered-Dose Inhalers and Valved Holding Chambers

Pressurized metered-dose inhalers deliver micronized drug crystals dissolved or suspended within a liquefied propellant alongside co-solvents, such as ethanol, and surfactant stabilizers [73]. Actuation releases a calibrated liquid volume via a spring-loaded metering valve, disintegrating into an aerosol plume as the volatile propellant flashes [74].

6.1.1. Physical and Operational Mechanisms:

Standard pMDIs generate high initial plume velocities exceeding 30 m/s over brief release times under 0.2 seconds. Poor hand-breath coordination causes the majority of the dose to impact the posterior oropharynx, while rapid propellant evaporation can trigger the cold-Freon reflex that halts inspiration [75].

6.1.2. Breath-Actuated Systems (baMDIs)

Incorporating an internal mechanical vane primed by opening the cap, baMDIs fire automatically when inspiratory airflow exceeds roughly 20 to 30 L/min, eliminating the need for manual coordination [76].

6.1.3. Valved Holding Chambers and Spacers

Placing a valved holding chamber between the pMDI actuator and the patient decreases plume velocity, allows propellant evaporation, and retains non-respirable ballistic droplets, thereby mitigating oropharyngeal deposition and improving peripheral lung fraction [77].

6.2. Dry Powder Inhalers

Dry powder inhalers provide propellant-free, solid-state pharmaceutical formulations actuated directly by the patient's inspiratory effort [78]. The internal formulation typically contains micronized drug particles measuring 1 to 5 μm blended with coarse carrier crystals, predominantly α-lactose monohydrate measuring 50 to 200 μm [79].

6.2.1. Dispersion Mechanisms:

The coarse carrier enhances bulk powder flow and filling accuracy. During inhalation, fluid shear forces and turbulent collisions within the device break the adhesive bonds between drug and carrier: coarse lactose impacts the oropharynx, whereas the liberated active drug penetrates into peripheral airways [80].

6.2.2. Operational Flow Resistance

DPIs are engineered across various internal resistance categories. Achieving effective powder de-agglomeration requires patients to generate an adequate peak inspiratory flow rate (typically ≥ 30--60 L/min) along with a sharp initial pressure drop [81]. Severe airflow obstruction or respiratory muscle fatigue can compromise de-agglomeration efficiency, and environmental moisture exposure may lead to particle clumping.

6.3. Soft Mist Inhalers

Soft mist inhalers generate unpressurized, aqueous drug clouds without requiring chemical propellants [82]. The mechanical design utilizes internal spring tension to force a metered volume of drug solution through colliding microchannels, producing a slow-moving aerosol plume [83].

The generated plume moves at roughly 0.8 m/s with a generation duration lasting between 1.2 and 1.5 seconds. This prolonged velocity profile decreases oropharyngeal impaction and yields pulmonary deposition rates often exceeding 40% to 50% of the nominal dose, even in patients with compromised coordination [84]. The delivered dose remains limited by drug solubility within the small aqueous metered volume (10 to 15 μL) [85].

6.4. Ultrasonic, Jet, and Vibrating Mesh Nebulizers

Nebulizers transform liquid pharmaceutical solutions or suspensions into respirable mists suitable for passive tidal breathing, proving particularly useful in acute exacerbations or non-ambulatory care [86]:

6.4.1. Pneumatic Jet Nebulizers

Employ compressed gas via a Venturi orifice to draw and shear bulk liquid against internal baffles, yielding respirable droplets alongside significant dead volume and operational noise [87].

6.4.2. Ultrasonic Nebulizers

Use high-frequency piezoelectric vibrations (1–3 MHz) to produce surface capillary waves, though local heating risks degrading heat-sensitive proteins and liposomal structures.

6.4.3. Vibrating Mesh Nebulizers

Drive liquid through an electroformed membrane containing thousands of laser-drilled funnel-shaped micro-apertures vibrating at 100 to 130 kHz. This platform maintains macromolecular stability, minimizes residual volume (< 0.2 mL), and ensures consistent aerosol delivery across quiet tidal respiration [88]. The operational parameters, structural benefits, and mechanical limitations across the primary clinical inhalation platforms are summarized in Table 1.

Table 1. Comparison of Pulmonary Inhalation Devices

Inhaler Type	Formulation	Dispersion / Metering Mechanism	Examples	Clinical Advantages	Limitations
Pressurized Metered-Dose Inhaler (pMDI)	Drug dissolved or suspended in liquefied hydrofluoroalkane propellant (HFA-134a or HFA-227), often with ethanol and surfactants.	Metering valve (typically 25–100 μ L) discharging through an atomizing actuator orifice upon manual depression.	Evohaler, Airomir, ProAir, Atrovent pMDI.	Compact, uniform multi-dose metering, rapid administration, low dependency on patient peak inspiratory flow rate.	Demands precise manual hand-breath coordination; high initial plume velocity induces oropharyngeal impaction; susceptibility to cold-Freon reflex.
pMDI with Valved Holding Chamber (VHC)	Suspended or dissolved drug droplets delivered into an auxiliary spacer chamber.	Metered discharge into a sealed chamber; inhalation regulated via one-way silicone inspiratory valves.	AeroChamber Plus, OptiChamber Diamond, Volumatic, Vortex.	Decouples device actuation from patient inspiration; promotes propellant evaporation; mitigates oropharyngeal impaction; enhances peripheral lung deposition.	Bulkier footprint; requires regular cleaning to avoid electrostatic charge build-up; potential for drug retention on interior chamber surfaces.
Breath-Actuated MDI (baMDI)	Micronized drug particles suspended in propellant with stabilizing excipients.	Spring-actuated release mechanism triggered mechanically when patient inspiratory flow exceeds threshold.	Autohaler, Easi-Breathe.	Eliminates manual coordination errors; fires reliably at low inspiratory flow rates (~20–30 L/min); well-suited for patients with arthritic joint limitations.	Limited range of available drug formulations; retains the plume characteristics and cold-Freon effects of volatile propellants.
Dry Powder Inhaler (DPI)	Micronized crystalline drug combined with coarse carrier particles (e.g., lactose monohydrate) or engineered carrier-free porous microparticles.	Inspiratory-driven fluidization and de-agglomeration through tortuous internal flow paths, grids, and swirl chambers.	Diskus, Turbuhaler, HandiHaler, Breezhaler, Ellipta, Nexthaler.	Propellant-free formulation; breath-actuated; stable solid-state compositions; convenient multi-dose or single-dose blister configurations.	Dependent on patient's peak inspiratory effort ($PIFR \geq 30$--60 L/min) to de-agglomerate particles; susceptible to environmental moisture; variable dosing during acute exacerbations.
Soft Mist Inhaler (SMI)	Aqueous drug solution or micro-suspension; preservative-free, propellant-free.	Mechanical spring tension pushes liquid through a micro-engineered nozzle array, generating two colliding fluid jets.	Respimat.	Slow-moving aerosol plume (0.8 m/s) with a long generation time (1.2–1.5 s); high fine-particle fraction; enhanced lung deposition;	Metered dose limited by liquid volume (10--15 μL) and drug aqueous solubility; requires manual priming and spring-loading rotation before actuation.
Vibrating Mesh Nebulizer (VMN)	Pure aqueous solutions, liposomal dispersions, or macromolecular suspensions.	Piezoelectric transducer vibrates a micro-perforated mesh (100–130 kHz), drawing liquid through micrometer-sized apertures.	Aeroneb, eFlow Rapid, MicroAir NE-U22.	Operates during tidal breathing without coordination; minimal residual volume (< 0.2 mL); no propellant; does not generate heat; suitable for proteins and liposomal carriers.	Higher acquisition cost; requires regular cleaning and sterilization to avoid aperture clogging and microbial contamination; requires an electrical power source.

7. Advances in Formulation Techniques and Macromolecular Delivery

7.1. Large Porous Particles and Pulmospheres

Formulation science has moved beyond traditional micronization to design engineered particles with optimized aerodynamic performance [89]. Standard compact micronized particles measuring 1 to 3 μm often exhibit strong cohesive forces, causing them to clump together and deposit prematurely within delivery devices or upper airways.

To overcome this, emulsion-based spray-drying techniques are used to formulate large porous particles, known as Pulmospheres [90]. These particles possess geometric diameters between 5 and 20 μm while maintaining low mass densities below 0.1 g/cm^3. The mass median aerodynamic diameter (d_{ae}) is governed by the geometric diameter (d_g), the particle density (ρ), and the shape factor (χ):

$$d_{ae} = d_g \sqrt{\frac{\rho}{\rho_0 \chi}}$$

Because particle density remains low, these microstructures behave aerodynamically like standard 1 to 3 μm spheres, facilitating deep alveolar penetration. Their larger physical size suppresses particle-particle cohesion by lowering contact points, enhancing powder fluidization within DPI systems while evading recognition and clearance by alveolar macrophages [91].

Table 2. Formulations and Nanotechnology Platforms for Pulmonary Drug Delivery

Formulation	Nanotechnology / Carrier Category	Physicochemical Properties and Mechanisms	Targeted Respiratory and Systemic Applications
Colloidal Lipid Nanocarriers	Solid Lipid Nanoparticles (SLN), Nanostructured Lipid Carriers (NLC), Liposomal Vesicles.	Phospholipid bilayers or solid lipid matrices stabilized by non-ionic surfactants; high encapsulation efficiency for hydrophobic drugs; integrates with pulmonary surfactant.	Sustained release of inhaled corticosteroids, targeted bronchodilation, and localized antimicrobial delivery for pulmonary infections.
Biodegradable Polymeric Systems	PLGA micro/nanoparticles, Poly(lactic acid) (PLA), Chitosan conjugates.	Hydrolytically degradable polymeric backbones; controlled drug diffusion; positive surface functionalization via amine groups enhances mucosal retention.	Sustained anti-inflammatory depot delivery, vascular remodeling inhibition, and controlled cytokine antagonist release.
Engineered Porous Microparticles	Pulmospheres, spray-dried hollow porous microstructures.	Low tapped density ($\rho < 0.1$ g/cm^3), high geometric diameter (5--15 μm), low aerodynamic diameter (1--3 μm); reduced van der Waals attraction.	High-efficiency DPI powder dispersion, long retention in deep lung airspaces, and evasion of alveolar macrophage clearance.
Dry Powder Carrier Blends	Ternary interactive mixtures, conditionally engineered α-lactose monohydrate, spray-dried mannitol.	Micronized active pharmaceutical ingredients linked to coarse crystalline sugars; addition of fine carrier fractions or magnesium stearate reduces surface energy.	Modern maintenance combination therapies (LABA/LAMA/ICS) utilizing dry powder inhalation systems.
Macromolecular and Biologic Aerosols	Therapeutic peptides, monoclonal antibody fragments, mRNA lipid nanoparticles, siRNA.	Lyophilized or spray-freeze-dried biomolecules stabilized by amorphous disaccharides (trehalose, sucrose); uptake via transcellular transcytosis.	Replacement therapy for alpha-1 antitrypsin deficiency, targeted immunomodulation, and localized gene therapies for chronic lung diseases.
Stimuli-Responsive Nanogels	pH-responsive, matrix metalloproteinase (MMP)-cleavable crosslinked polymers.	Polymeric matrices that swell or degrade in response to acidic microenvironments or elevated proteolytic enzyme levels in inflamed COPD tissues.	On-demand anti-inflammatory and antioxidant release localized to active tissue remodeling sites.

7.2. Biodegradable Polymeric and Lipid Nanocarriers

Polymeric nanoparticles engineered from biocompatible polymers, such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone, and chitosan, offer sustained release of encapsulated bronchodilators and anti-inflammatory molecules [92]. Polymeric nanoparticles protect therapeutic agents from enzymatic degradation within the lung lining fluid while facilitating sustained release via ester bond hydrolysis. Solid lipid nanoparticles and nanostructured lipid carriers prepared with physiological lipids provide high entrapment efficiency for poorly water-soluble compounds, prolonging retention within target tissues.

7.3. Pulmonary Liposomal Systems

Liposomes are spherical vesicles composed of concentric phospholipid bilayers surrounding an aqueous core, historically developed to treat neonatal respiratory distress syndrome by replenishing endogenous surfactant levels [93]. Formulations containing synthetic phospholipids like dipalmitoylphosphatidylcholine integrate smoothly with alveolar surfactant films. Inhaled liposomal suspensions encapsulate both hydrophilic molecules within their central core and lipophilic compounds within their lipid bilayers, providing sustained drug release and reducing mucosal irritation [94].

7.4. Inhalable Biological agents, Peptides, and Gene Vectors

The high vascularization and non-destructive transcytosis pathways of the deep lung make the pulmonary route viable for delivering complex therapeutic peptides, recombinant proteins, and nucleic acid therapies [95]. Formulating these delicate macromolecules requires protective spray-freeze-drying techniques with stabilizing sugars, such as trehalose and mannitol, to prevent thermal denaturation during aerosolization. Current molecular platforms include mRNA encapsulated in lipid nanoparticles and synthetic small interfering RNAs engineered to downregulate pro-inflammatory cytokines, mucus-hypersecretion pathways, and remodeling enzymes in COPD [96]. Recent developments in aerosol formulation platforms, carrier architectures, and functional applications are outlined in Table 2.

8. Device Selection, Patient Adherence, and Digital Monitoring

The real-world success of inhaled pharmacotherapy relies heavily on matching device mechanics to patient physical abilities and ensuring consistent technique [97]. Critical errors during inhaler use are widespread among COPD patients, often driven by cognitive decline, reduced visual acuity, muscle weakness, or limited inspiratory capacity.

8.1. Matching Devices to Patient Profiles

A patient with severe dynamic hyperinflation and reduced inspiratory effort may struggle to generate the peak inspiratory flow rate necessary to de-agglomerate a high-resistance dry powder inhaler. In these cases, moving to a soft mist inhaler, a breath-actuated MDI, or a vibrating mesh nebulizer provides consistent drug delivery independent of inspiratory effort [98]. Conversely, for patients with preserved inspiratory flow who have trouble coordinating manual actuation with inhalation, breath-actuated DPIs or pMDIs paired with valved holding chambers minimize coordination errors.

8.2. Impact on Clinical Outcomes

Observational studies confirm that improper inhaler technique directly correlates with poor symptom control, increased emergency room visits, and higher rates of severe acute exacerbations [99]. Routine physical demonstration, structured patient education, and periodic reassessments of inhaler handling are critical components of pulmonary disease management.

8.3. Digital Inhalers and Sensors

The development of electronic inhalers featuring integrated acoustic sensors, optical encoders, and Bluetooth connectivity allows real-world monitoring of inhaler adherence. These connected devices record actuation timestamps, verify inspiratory flow profiles, and assess breath-holding times. Providing real-time feedback through mobile health applications helps patients refine their inhalation technique, allows clinicians to detect declining compliance early, and enables data-driven adjustments to therapeutic regimens.

9. Conclusion

Targeted pulmonary drug delivery is a core strategy in the management of chronic obstructive pulmonary disease and complex respiratory disorders. Delivering pharmacological agents directly to the tracheobronchial and alveolar surfaces achieves high local therapeutic concentrations, reduces off-target systemic exposure, and avoids hepatic first-pass metabolism. Effectively navigating anatomical barriers, such as airway branching, mucociliary transport, and alveolar macrophage clearance, requires coordinated development across particle physics, formulation engineering, and inhaler hardware. Advances in large porous microparticles, lipid

and polymeric nanocarriers, and responsive biomaterials have improved aerosol dispersion and enabled sustained drug release in deep lung tissues. Similarly, device innovations, such as soft mist inhalers, vibrating mesh nebulizers, and digital monitoring systems, help overcome traditional handling errors and expand access for diverse patient populations. Developing scalable manufacturing methods for inhalable macromolecules, refining targeted nano-therapies, and leveraging digital technologies to support proper inhaler use will enhance clinical outcomes and quality of life for individuals with chronic respiratory conditions.

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