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Review Article

Inhalable Nanocarriers for Pulmonary Drug Delivery Systems: A Comprehensive Review

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ABSTRACT

Pulmonary drug delivery has emerged as a promising approach for the treatment of respiratory and systemic diseases due to the unique anatomical and physiological characteristics of the lungs, including a large surface area, extensive vascularization, and rapid drug absorption. However, conventional inhalation systems such as metered dose inhalers, dry powder inhalers, and nebulizers often suffer from limitations including poor lung deposition, rapid mucociliary clearance, low bioavailability, and reduced therapeutic efficiency. In recent years, inhalable nanocarriers have gained considerable attention as advanced pulmonary drug delivery platforms capable of overcoming these challenges. These nanosized systems, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, micelles, and nanoemulsions, offer advantages such as enhanced lung retention, controlled drug release, improved mucus penetration, and targeted delivery. This review comprehensively discusses the anatomy and physiology of the respiratory tract, mechanisms of particle deposition, formulation strategies, and characterization techniques associated with inhalable nanocarriers. Furthermore, their therapeutic applications in asthma, chronic obstructive pulmonary disease, tuberculosis, lung cancer, cystic fibrosis, pulmonary fibrosis, and viral infections are highlighted. The review also addresses safety concerns, nanotoxicity, clinical translation, regulatory considerations, and emerging future perspectives including smart inhalers, personalized nanomedicine, and AI-assisted formulation development. Overall, inhalable nanocarriers represent a promising strategy for advancing next-generation pulmonary therapeutics.

INTRODUCTION

1.1 Overview of Pulmonary Drug Delivery

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The pulmonary route for drug administration has been recognized for centuries, with early records of medicinal smoke inhalation in ancient Egyptian and Indian medicine. However, the modern era of pulmonary drug delivery began in the mid-20th century with the introduction of pressurized metered-dose inhalers (pMDIs) by Riker Laboratories in 1956, which revolutionized asthma management. Subsequent decades witnessed significant advances in inhaler device technology, drug formulation, and understanding of aerosol science, culminating in a diverse portfolio of inhaled therapeutics available today[1].

Pulmonary drug delivery serves a dual therapeutic purpose: local delivery for respiratory diseases such as asthma, COPD, and pneumonia, and systemic delivery exploiting the lungs as an absorptive portal[2]. The latter strategy is exemplified by inhaled insulin (Exubera, Afrezza), demonstrating the lungs' capacity for systemic delivery of macromolecules. The alveolar region, with its enormous surface area (~100 m^2), ultra-thin epithelium (~0.2 μm), and intimate proximity to ~280 billion capillaries, facilitates rapid systemic absorption and bypasses hepatic first-pass metabolism, offering pharmacokinetic advantages over oral administration[3].

1.2 Burden of Respiratory Diseases

Respiratory diseases constitute a major global health burden, collectively affecting hundreds of millions of individuals worldwide and contributing significantly to morbidity and mortality. The World Health Organization (WHO) identifies chronic respiratory diseases among the leading causes of death globally, with an estimated 3 million deaths per annum attributable to COPD alone[4].

Asthma affects approximately 300 million people globally, with rising prevalence in low- and middle-income countries due to urbanization, air pollution, and changing allergen exposures. COPD, primarily caused by cigarette smoking and biomass fuel exposure, is projected to become the third leading cause of death worldwide by 2030[5]. Pulmonary tuberculosis remains one of the deadliest infectious diseases, claiming over 1.5 million lives annually, with the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains posing unprecedented therapeutic challenges. Lung cancer is the leading cause of cancer-related mortality worldwide, with over 2 million new cases diagnosed annually, underscoring the urgent need for targeted inhalation-based chemotherapeutic strategies. Pulmonary fibrosis, particularly idiopathic pulmonary fibrosis (IPF), carries a median survival of only 2–5 years post-diagnosis, and currently approved antifibrotic agents (pirfenidone, nintedanib) offer only modest benefit. The COVID-19 pandemic, caused by SARS-CoV-2, has highlighted the vulnerability of the respiratory system to emerging pathogens and renewed interest in inhaled antiviral therapeutics and mucosal vaccines[6].

1.3 Limitations of Conventional Pulmonary Drug Delivery

Despite the therapeutic potential of the inhalation route, conventional pulmonary delivery systems are hampered by several critical limitations[7,8,9]. First, poor lung deposition efficiency is a pervasive challenge; most commercial MDIs deliver only 10–40% of the nominal dose to the lung, with the remainder depositing in the oropharynx or the device itself. Second, once deposited in the airways, inhaled drugs face rapid elimination by the mucociliary escalator, which propels mucus and entrapped particles from the conducting airways toward the pharynx within 24 hours. This mechanism, while protective against

pathogens, significantly reduces drug residence time and bioavailability[10].

Third, in the alveolar region, alveolar macrophages (AMs) phagocytose deposited particles through a size-dependent mechanism, rapidly internalizing particles >1 μm. Fourth, enzyme-mediated drug degradation by proteases, esterases, and cytochrome P450 enzymes present in respiratory secretions and epithelial cells can reduce drug potency before systemic absorption[11]. Fifth, the epithelial tight junctions of the bronchial epithelium restrict paracellular drug transport. Sixth, patient compliance with complex inhaler techniques is suboptimal, particularly among pediatric, geriatric, and acutely dyspnoeic patients. These limitations collectively highlight the need for advanced drug delivery strategies capable of overcoming pulmonary barriers[12].

1.4 Emergence of Nanotechnology in Pulmonary Delivery

Nanotechnology offers a paradigm shift in overcoming the inherent limitations of conventional pulmonary drug delivery. Nanocarriers defined as delivery systems with at least one dimension in the 1–1000 nm range possess unique physicochemical properties, including high surface-area-to-volume ratio, tunable surface chemistry, and enhanced cellular interactions, that confer distinct advantages for pulmonary applications. Their nanoscale dimensions allow them to evade mucociliary clearance, penetrate mucus barriers, avoid alveolar macrophage phagocytosis (for particles < 200 nm), and achieve prolonged drug residence in the lungs[13,14].

Furthermore, surface functionalization of nanocarriers with targeting ligands (antibodies, aptamers, receptor-specific peptides) enables active targeting to specific cell populations within the lungs, including type II pneumocytes, macrophages, and tumor cells. Stimuli-responsive nanocarriers designed to release drug payloads in response to pathological microenvironmental cues (e.g., acidic pH in infected or cancerous tissue, elevated reactive oxygen species in inflamed airways) represent a further evolution toward intelligent, site-specific pulmonary therapy[15,16].

1.5 Scope and Objectives of the Review

This review provides a comprehensive and up-to-date appraisal of inhalable nanocarriers for pulmonary drug delivery. The primary objectives are: (i) to outline the anatomy and physiology of the respiratory tract with emphasis on barriers relevant to drug delivery; (ii) to classify and characterize the principal types of inhalable nanocarriers; (iii) to describe key formulation strategies and characterization techniques; (iv) to review therapeutic applications of inhalable nanocarriers across major respiratory diseases; (v) to assess nanotoxicological considerations and strategies for mitigation; (vi) to discuss the regulatory landscape and clinical translation pathway; and (vii) to identify emerging trends and future directions in pulmonary nanomedicine. By integrating current literature with mechanistic insights, this review aims to serve as an authoritative reference for pharmaceutical scientists, clinicians, and regulatory professionals engaged in pulmonary nanomedicine research.

2. ANATOMY AND PHYSIOLOGY OF THE RESPIRATORY SYSTEM:

2.1 Structure of the Respiratory Tract

The human respiratory tract is anatomically divided into the upper and lower respiratory tracts. The upper respiratory tract encompasses the nose,

nasal cavity, pharynx, and larynx, while the lower respiratory tract comprises the trachea, bronchi, bronchioles, and the alveolar region. Functionally, the respiratory tract is partitioned into the conducting zone (trachea to terminal bronchioles, generations 0–16) and the respiratory zone (respiratory bronchioles, alveolar ducts, and alveolar sacs, generations 17–23)[17,18].

The tracheobronchial tree undergoes progressive dichotomous branching (Weibel model), increasing in total cross-sectional area from ~2.5 cm^2 at the trachea to ~11,800 cm^2 at the alveolar level[19]. The alveoli, numbering approximately 300–500 million in adult lungs, are the primary sites of gas exchange and systemic drug absorption. Their combined surface area of ~100 m^2, lined by a thin (0.1–0.2 μm) alveolar epithelium covered with pulmonary surfactant, creates an ideal environment for rapid drug dissolution and absorption[20].

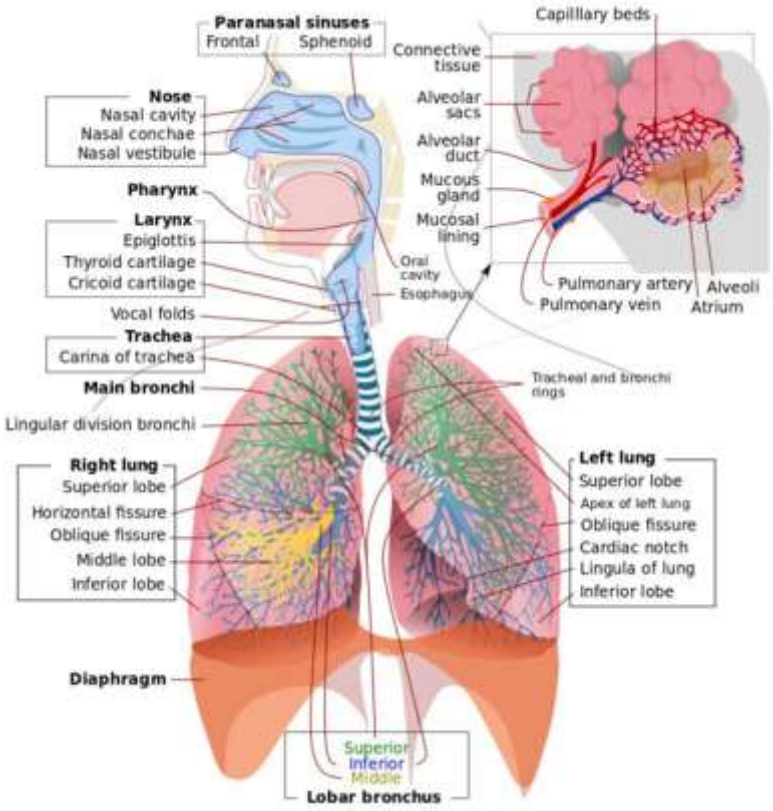

Figure 1. Anatomy of the Human Respiratory System Showing Upper and Lower Respiratory Tract, Bronchial Tree, and Alveolar Region

2.2 Lung Physiology Relevant to Drug Delivery

The efficiency of inhaled drug delivery is governed by several physiological parameters. Airflow dynamics within the respiratory tract are predominantly turbulent in the upper airways (high velocity, large caliber), transitioning to laminar flow in the smaller bronchioles and alveoli. Turbulent flow promotes inertial impaction of larger particles in the oropharynx and upper airways, while laminar flow facilitates sedimentation and diffusion of smaller particles in the alveolar region[21].

The alveolar epithelium consists predominantly of type I pneumocytes (~95% of alveolar surface area), which are thin, squamous cells optimized for gas exchange, and type II pneumocytes (~5% of

surface area), which are cuboidal, surfactant-secreting cells with high metabolic activity and receptor expression. The pulmonary surfactant monolayer, composed primarily of phosphatidylcholine (~45%), phosphatidylglycerol (~8%), and surfactant proteins (SP-A, SP-B, SP-C, SP-D), plays a pivotal role in reducing alveolar surface tension and in the interaction with inhaled nanoparticles[22].

2.3 Pulmonary Barriers Affecting Drug Delivery

Drug-laden particles and nanocarriers deposited in the respiratory tract encounter a cascade of formidable biological barriers. The mucus barrier, produced by goblet cells and submucosal glands throughout the conducting airways, forms a viscoelastic gel layer 5–100 µm thick that traps inhaled particles and is continuously transported to the oropharynx by ciliary action at ~4–6 mm/min. The mucus is composed of highly glycosylated mucin glycoproteins (MUC5AC, MUC5B) that create a dense polymer mesh with pore sizes of ~200 nm, significantly impeding the diffusion of conventional nanoparticles[23,24].

Alveolar macrophages (AMs), resident immune sentinels of the alveolar space, constitute the primary cellular defense mechanism against inhaled particles. AMs efficiently phagocytose particles with aerodynamic diameters of 1–6 µm, leading to lysosomal drug degradation and particle clearance from the lungs within hours to days. Enzymatic degradation in the airway lining fluid and within intracellular compartments further reduces drug bioavailability. Tight junctions between airway epithelial cells (claudin-3, claudin-4, occludin, ZO-1) restrict paracellular drug permeation, particularly for hydrophilic macromolecules[25,26].

2.4 Mechanisms of Particle Deposition

The regional deposition of inhaled particles in the respiratory tract is governed by three primary physical mechanisms. Inertial impaction is the dominant mechanism for particles with aerodynamic diameter > 5 µm and is responsible for deposition at bifurcations and bends in the upper airways, where rapidly moving particles cannot follow airstream changes[27]. Gravitational sedimentation predominates for particles with aerodynamic diameter between 1 and 5 µm in the smaller bronchioles and alveolar region, where residence time is prolonged and airflow velocity is low. Diffusion (Brownian motion) is the primary deposition mechanism for ultrafine particles < 0.5 µm in diameter in the alveolar region, where convective flow is negligible[28].

The optimal aerodynamic diameter for deep lung deposition (alveolar targeting) lies within the range of 1–5 µm, as larger particles deposit in the oropharynx via impaction and sub-micron particles may be exhaled before depositing. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) are the key parameters describing the aerosol size distribution and are measured using cascade impaction[29].

Optimal aerodynamic diameter: 1 µm < da < 5 µm (Eq. 1)

$da = dg \times \sqrt{(\rho/\rho_0)}$ (Eq. 2 – Aerodynamic diameter equation)

where da is the aerodynamic diameter, dg is the geometric diameter, ρ is the particle density, and ρ_0 is the unit density (1 g/cm³). Particle density is a critical formulation parameter; low-density particles (e.g., porous particles, hollow microspheres) with large geometric diameters but small aerodynamic diameters can achieve deep

lung deposition while evading macrophage uptake[30].

Table 1: Relationship between particle size and deposition site in the respiratory tract

Aerodynamic Diameter	Deposition Region	Deposition Mechanism	Clinical Relevance
> 10 µm	Oropharynx, nasopharynx	Inertial impaction	Topical nasal/throat delivery
5–10 µm	Trachea, large bronchi	Impaction	Central airway disease
1–5 µm	Bronchioles, alveoli	Sedimentation, diffusion	Optimal for deep lung delivery
0.5–1 µm	Alveolar region	Sedimentation, diffusion	Alveolar macrophage evasion zone
< 0.5 µm	Alveolar region (exhaled)	Brownian diffusion	Significant exhalation loss

3. PULMONARY DRUG DELIVERY SYSTEMS:

3.1 Conventional Pulmonary Delivery Systems

Conventional pulmonary delivery systems form the therapeutic backbone of current inhaled pharmacotherapy. Pressurized metered-dose inhalers (pMDIs) consist of a pressurized canister containing drug formulation (solution or suspension) in a liquefied propellant (currently hydrofluoroalkanes, HFA-134a and HFA-227ea, following the phase-out of chlorofluorocarbons). Upon actuation, a metered valve releases a precise drug volume as an aerosol plume. Despite widespread use, pMDIs deliver only 10–30% of the nominal dose to the lungs due to high oropharyngeal deposition, and their effectiveness is critically dependent on proper hand-breath coordination[31,32].

Dry powder inhalers (DPIs) are breath-actuated devices delivering micronized drug powder, either as pure drug, drug-carrier blends (with lactose monohydrate), or engineered particles. DPIs overcome the coordination issues of pMDIs and eliminate propellants but require adequate inspiratory flow rates (typically > 30–60 L/min), limiting their utility in severe airflow obstruction and pediatric patients. Nebulizers convert aqueous drug solutions or suspensions into fine aerosol droplets using pneumatic (jet nebulizer), ultrasonic, or mesh/vibrating membrane mechanisms. While allowing high drug doses and requiring minimal patient effort, nebulizers have drawbacks including long treatment times, drug degradation (thermal/ultrasonic), and bulkiness[33,34].

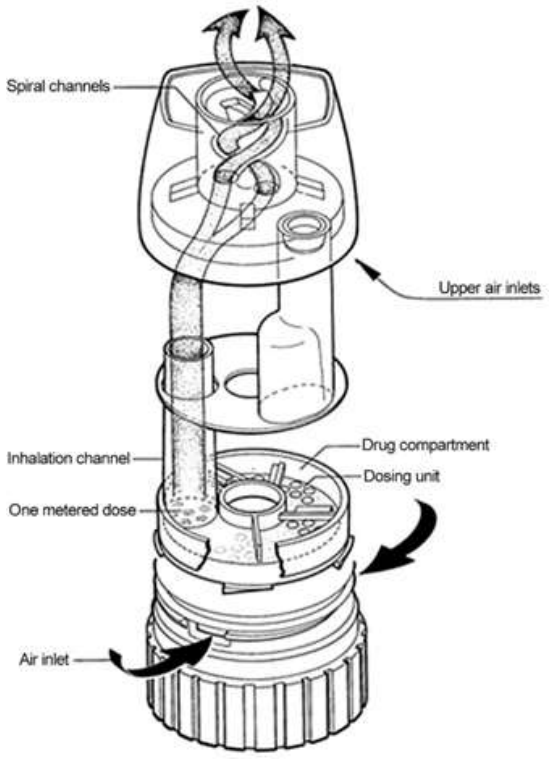

Figure 2. Schematic Representation of a Dry Powder Inhaler (DPI) Showing Airflow Pathway, Dosing Unit, and Powder Dispersion Mechanism

3.2 Advantages of the Pulmonary Route

The pulmonary route offers several distinctive pharmacokinetic and pharmacodynamic

advantages. The large surface area (~100 m²) and thin alveolar membrane facilitate rapid drug absorption with near-intravenous pharmacokinetics for some drugs. Avoidance of hepatic first-pass metabolism allows drugs with extensive pre-systemic metabolism (e.g., opioids, peptides) to achieve enhanced systemic bioavailability via inhalation. Direct delivery to the lungs maximizes local drug concentrations at the site of respiratory disease, enabling lower total doses and reduced systemic adverse effects compared to oral or parenteral administration[35].

3.3 Limitations of Conventional Delivery and Need for Nanocarrier-Based Systems

The limitations enumerated above poor and variable lung deposition, rapid mucociliary clearance, macrophage phagocytosis, enzymatic degradation, limited dose capacity, and patient compliance issues collectively constrain the therapeutic potential of conventional inhaled formulations. Additionally, conventional systems offer limited control over drug release kinetics, typically delivering drug in an immediate-release pattern, necessitating frequent dosing that adversely affects patient adherence. These unmet needs provide a compelling rationale for the development of nanocarrier-based inhalable formulations[36,37,38].

Table 2: Comparison of pulmonary drug delivery systems

System	Device Type	Particle Size	Key Feature
MDI	Pressurized canister	2–5 µm	Portable, propellant-driven
DPI	Breath-actuated	1–5 µm	No propellant, dose consistency
Nebulizer	Liquid aerosol generator	1–5 µm	High dose, for severe patients
Nano-DPI	Engineered nanoparticles	100–1000 nm	Sustained release, targeting
Soft mist inhaler	Aqueous spray	1–5 µm	Slow plume, high deposition

4. INHALABLE NANOCARRIERS: CLASSIFICATION AND CHARACTERISTICS:

Inhalable nanocarriers represent a structurally diverse class of nanoscale drug delivery platforms, each offering distinct advantages in drug loading, release kinetics, targeting capability, and stability. A thorough understanding of their composition, preparation, and biopharmaceutical properties is essential for rational formulation design[39,40].

4.1 Liposomes

Liposomes are spherical vesicular nanocarriers comprising one or more phospholipid bilayers enclosing an aqueous core, enabling simultaneous encapsulation of hydrophilic drugs (aqueous core), hydrophobic drugs (lipid bilayer), and amphiphilic molecules (lipid-water interface)[41,42]. Typical pulmonary liposomes are composed of phosphatidylcholines (DPPC, DSPC), phosphatidylglycerols (DPPG), and cholesterol, with sizes of 50–400 nm. PEGylated (stealth) liposomes bearing polyethylene glycol coatings exhibit prolonged circulation and reduced macrophage recognition through steric stabilisation; cationic liposomes (DOTAP, DOTMA) are extensively investigated for nucleic acid delivery. Preparation methods include thin-film hydration, solvent injection, extrusion, and supercritical fluid technology, with conversion to dry powder by spray drying or freeze drying for inhalation. Arikayce (liposomal amikacin inhalation suspension, ALIS), the first FDA-approved inhaled liposomal antibiotic (2018), demonstrates the clinical viability of liposomal pulmonary delivery[43,44].

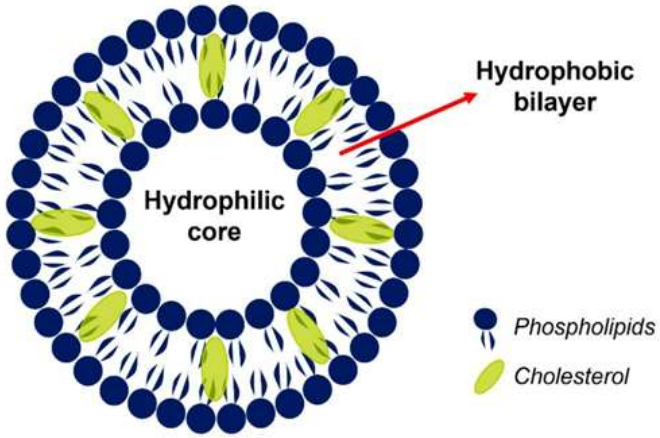

Figure 3. Structure of Liposomes

4.2 Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are solid or semi-solid colloidal systems categorised as nanospheres (matrix-type, drug distributed throughout the polymer) or nano capsules (reservoir-type, drug enclosed in a polymer shell). Poly(lactic-co-glycolic acid) (PLGA), an FDA-approved biodegradable copolymer that degrades hydrolytically to lactic acid and glycolic acid, offers highly controllable drug release over days to months through manipulation of MW, LA:GA ratio, and particle size. Chitosan, a cationic polysaccharide derived from chitin with inherent mucoadhesive properties mediated by electrostatic interactions with mucin glycoproteins, prolongs pulmonary drug residence and enhances paracellular permeation by reversible tight junction modulation.[44,68] Other polymers alginate (anionic, pH-sensitive), gelatin (enzymatically degradable), and polyethylenimine (PEI, highly cationic for gene delivery)also find pulmonary application[45,46].

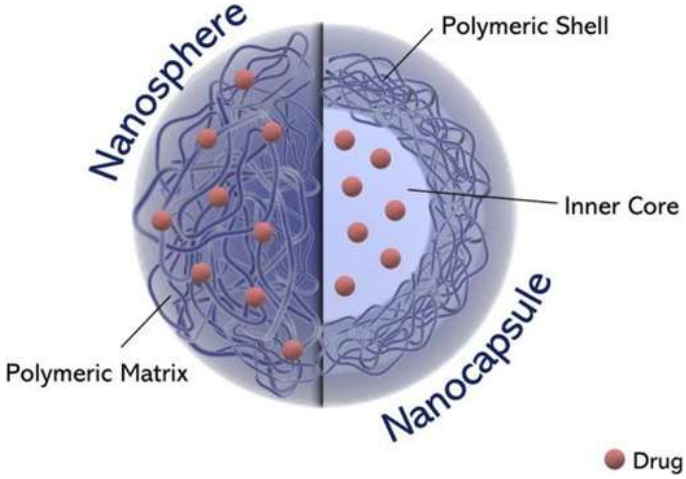

Figure 17. Polymeric Nanoparticles (Nanospheres and Nanocapsules)

4.3 Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

SLNs consist of a solid lipid matrix (glyceryl monostearate, glyceryl palmitostearate, stearic acid, acetyl palmitate) stabilised by surfactants (Tween 80, Poloxamer 188, lecithin); the solid-state matrix at body temperature provides a physical barrier to drug release, enabling sustained delivery[47]. Drug is incorporated via drug-enriched shell, drug-enriched core, or homogeneous matrix models. The main limitation

is polymorphic lipid transitions during storage (α→β crystal forms), leading to drug expulsion; SLNs are produced by high-pressure homogenisation, ultrasonication, microemulsion technique, or solvent emulsification-evaporation[48]. NLCs, developed as second-generation lipid nanoparticles, incorporate a blend of solid and liquid lipids (oleic acid, Miglyol 812, squalene at 0.5–30% of total lipid), creating a spatially imperfect crystal structure that provides greater drug accommodation, higher encapsulation efficiency, reduced drug expulsion, and improved stability compared to SLNs[49].

4.4 Dendrimers

Dendrimers are highly branched, three-dimensional macromolecules with a well-defined tree-like architecture comprising a central core, repeating branching units (generations), and numerous terminal functional groups; PAMAM and PPI dendrimers are most studied for biomedical applications. Their monodisperse nature (PDI ≈ 0), precisely tunable size (1–10 nm per generation), and multivalent surface functionality make them attractive for high drug payload delivery, surface functionalisation with targeting ligands, and nucleic acid complexation.[21] However, higher-generation cationic dendrimers exhibit concentration-dependent cytotoxicity, necessitating surface modification (PEGylation, acetylation) to reduce charge-mediated toxicity[50].

4.5 Nanoemulsions and Polymeric Micelles

Nanoemulsions are thermodynamically or kinetically stable colloidal dispersions of two immiscible liquids (typically oil-in-water for pulmonary use) stabilised by surfactant films, with droplet diameters of 20–500 nm; their small droplet size imparts superior drug solubilisation for hydrophobic drugs. Prepared by high-energy methods (high-pressure homogenisation, micro fluidisation) or low-energy methods (self-emulsification, phase inversion), they are particularly advantageous for BCS Class II/IV drugs, though physical instability (Ostwald ripening, droplet coalescence) during nebulisation remains a challenge[51]. Polymeric micelles are self-assembled nanostructures formed by amphiphilic block copolymers (PEG-PLA, PEG-PLGA, PEG-PCL, Pluronic's) in aqueous media above their critical micelle concentration (CMC), with a hydrophobic core (drug reservoir) and hydrophilic corona, typically 10–100 nm in diameter[51]. They have been investigated for pulmonary delivery of paclitaxel, curcumin, cyclosporine A, and voriconazole, demonstrating enhanced bioavailability and reduced systemic toxicity compared to free drug[52,53].

4.6 Metallic Nanoparticles and Hybrid Nanocarriers

Gold nanoparticles (AuNPs, 1–100 nm) are explored for pulmonary delivery due to facile surface functionalisation and photothermal therapy potential; silver nanoparticles (AgNPs) possess inherent antimicrobial activity against respiratory pathogens; mesoporous silica nanoparticles (MSNs, 50–300 nm) offer extremely high surface area (up to 1000 m^2/g) and large pore volume for high drug loading and stimuli-responsive release[54,55]. However, inorganic nanoparticles raise significant toxicological concerns including bio persistence, oxidative stress induction, and chronic inflammation upon long-term pulmonary exposure. Hybrid lipid-polymer nanoparticles (LPHNPs) integrate the biocompatibility of lipid shells with the structural integrity and controlled release of polymeric cores; stimuli-responsive hybrid nano systems exploiting pH (poly(methacrylic acid), chitosan), ROS (thioketal, boronate ester linkages), or enzyme-

responsive (MMP-2, MMP-9, hyaluronidase) mechanisms enable site-specific drug release in the pulmonary disease microenvironment[56,57].

Table 3: Classification of inhalable nanocarriers with key characteristics

Nanocarrier	Size Range	Core Material	Key Applications
Liposomes	50–400 nm	Phospholipids, cholesterol	Antibiotics, anticancer, gene delivery
Polymeric NPs	100–500 nm	PLGA, chitosan, alginate	TB, asthma, lung cancer
SLNs	50–1000 nm	Solid lipids (glyceryl palmitostearate)	COPD, controlled release
NLCs	100–500 nm	Solid + liquid lipids	Improved drug loading vs SLNs
Dendrimers	1–10 nm	PAMAM, PPI	Gene/siRNA delivery, targeting
Nanoemulsions	100–500 nm	Oil-in-water emulsion	Hydrophobic drug solubilization
Micelles	10–100 nm	Amphiphilic block copolymers	Poorly soluble drug delivery
Metallic NPs	1–100 nm	Gold, silver, silica	Imaging, theranostics (toxicity concern)
Hybrid NPs	100–400 nm	Lipid-polymer hybrids	Stimuli-responsive, multifunctional

Table 4: Advantages and limitations of major nanocarrier types

Nanocarrier	Advantages	Disadvantages	Stability Concerns
Liposomes	Biocompatible, surface-functional Zable, versatile	Short shelf life, production scalability	Hydrolysis, oxidation of lipids
PLGA NPs	FDA-approved polymer, controlled release	Acidic microenvironment on degradation	Moisture-sensitive
Chitosan NPs	Mucoadhesive, cationic, biodegradable	pH-dependent solubility	Relatively stable
SLNs	High drug loading, scalable production	Drug expulsion on storage	Polymorphic transitions
NLCs	Better drug loading than SLNs, flexible	Complex formulation	More stable than SLNs
Dendrimers	Monodisperse, high surface area	Cytotoxicity at high generations	Good stability

5. FORMULATION STRATEGIES FOR INHALABLE NANOCARRIERS:

Conversion of nanocarrier dispersions into inhalable dosage forms requires specialised manufacturing processes that preserve nanocarrier integrity, achieve appropriate aerodynamic particle characteristics, and maintain drug stability. The manufacturing method profoundly influences particle morphology, size distribution, aerodynamic performance, and long-term stability[58].

5.1 Spray Drying

Spray drying is the most widely employed technique for producing inhalable nanocarrier-based dry powders, involving atomisation of a nanoparticle dispersion into fine droplets via a two-fluid or ultrasonic nozzle, followed by rapid solvent evaporation in a heated drying chamber and cyclone collection[59]. Critical process parameters include inlet temperature (80–220°C), feed flow rate, aspirator rate, and spray gas flow rate. Excipients such as lactose, mannitol, trehalose, and leucine are incorporated as bulking agents and aerosolisation enhancers; L-leucine migrates to the particle surface during drying, forming a crystalline shell that improves powder dispersibility and reduces hygroscopicity. The

technique is scalable and produces particles in the optimal 1–5 µm MMAD range for deep lung deposition[60].

5.2 Freeze Drying (Lyophilisation)

Lyophilisation involves freezing the nanoparticle dispersion followed by sublimation of ice under reduced pressure, yielding a solid cake that can be reconstituted or further processed into dry powder[61]. It preserves the structural integrity of fragile nanocarriers (liposomes, protein-loaded particles) that may be destabilised by the thermal and mechanical stresses of spray drying. Cryoprotectants such as trehalose (optimally 1:5 w/w with lipid for liposomes), sucrose, and mannitol prevent liposome fusion and nanoparticle aggregation during freezing. The lyophilisation cycle comprising freezing (−40 to −80°C), primary drying (0.1–1 mbar, −20 to 0°C shelf temperature), and secondary drying (20–40°C)must be carefully optimised to achieve complete moisture removal (residual moisture <1%)[62,63].

5.3 Supercritical Fluid Technology and Nano Spray Drying

Supercritical fluid (SCF) technology exploits CO_2 above its critical point (31.1°C, 73.8 bar) to achieve liquid-like density but gas-like diffusivity; primary approaches include Rapid Expansion of Supercritical Solutions (RESS), Supercritical Anti-Solvent precipitation (SAS), and Gas Anti-Solvent (GAS), producing narrow particle size distributions and avoiding organic solvent residues particularly suitable for thermolabile and moisture-sensitive drugs[64]. Nano spray drying (NSD) employs piezoelectric vibration to generate extremely fine droplets (1–5 µm), enabling production of nanoparticles <500 nm with near-100% yield beyond the capability of conventional spray drying making it particularly suitable for high-value peptide, protein, and oligonucleotide formulations[65].

5.4 Particle Engineering and Critical Quality Parameters

Porous particle technology produces hollow or porous microparticles with large geometric diameters (5–30 µm) but low particle densities (<0.4 g/cm³), yielding aerodynamic diameters in the optimal 1–5 µm range while evading macrophage uptake. PulmoSphere® technology exemplifies this approach, using perfluorooctyl bromide as a blowing agent to produce low-density porous microparticles with superior aerosolisation efficiency. Critical physicochemical parameters for inhalable nanocarrier characterisation include: primary nanoparticle size (100–500 nm), aerodynamic diameter (1–5 µm MMAD), zeta potential (>±30 mV for colloidal stability), encapsulation efficiency (>70%), powder flowability (Carr index, Hausner ratio), and moisture content (<3% for DPI formulations)[66].

Table 5: Formulation methods for inhalable nanocarriers

Method	Principle	Advantages	Nanocarrier Types
Spray Drying	Atomization into hot air stream; rapid solvent evaporation	Scalable, continuous process, tunable particle size	Polymeric NPs, liposomes, SLNs
Freeze Drying	Lyophilization; sublimation of water from frozen product	Preserves fragile structures, good stability	Liposomes, protein-loaded NPs
Nano Spray Drying	Piezoelectric vibration of liquid to fine droplets	Particles < 500 nm, low material loss	Polymeric NPs, dendrimers
Supercritical Fluid	CO2 above critical point as solvent/antisolvent	No organic residue, narrow PSD	PLGA NPs, SLNs

Emulsification	Solvent displacement or emulsion-diffusion	Simple, versatile	Polymeric NPs, nanoemulsions
High Pressure Homogenization	Intense mechanical disruption under high pressure	Large-scale production, narrow size distribution	SLNs, NLCs

6. CHARACTERISATION OF INHALABLE NANOCARRIERS:

6.1 Physicochemical and Morphological Characterisation

Particle size and size distribution the most fundamental parameters are determined by dynamic light scattering (DLS, providing hydrodynamic diameter [Z-average] and polydispersity index [PDI]; PDI <0.3 indicates monodispersity), nanoparticle tracking analysis (NTA, providing particle-by-particle tracking for 50–2000 nm), or laser diffraction. The zeta potential, measured by laser Doppler electrophoresis, provides information on surface charge and colloidal stability; values >±30 mV indicate sufficient electrostatic repulsion. Morphological analysis is performed by scanning electron microscopy (SEM, for surface topography of spray-dried particles), transmission electron microscopy (TEM/cryo-TEM, for internal structural information at near-native hydration), and atomic force microscopy (AFM, for nanoscale topographic mapping and mechanical properties)[67,68].

6.2 Aerosol Performance, Drug Release, and Stability

In vitro aerosol performance characterisation employs pharmacopoeial cascade impaction methods (Ph.Eur., USP) using the Andersen Cascade Impactor (ACI) or Next Generation Impactor (NGI) to determine: Mass Median Aerodynamic Diameter (MMAD), Geometric Standard Deviation (GSD), Fine Particle Fraction (FPF, % dose with aerodynamic diameter <5 µm), Fine Particle Dose (FPD), and Emitted Dose (ED). High-quality inhalable formulations target MMAD of 1–5 µm and FPF >35%. In vitro drug release is studied using Franz diffusion cells, dialysis bag methods, or simulated lung fluid (SLF) systems (Gamble's solution, SLF-I/II); release profiles are modelled using zero-order, first-order, Higuchi, or Korsmeyer-Peppas models. Stability evaluation encompasses physicochemical stability under ICH-recommended conditions (25°C/60% RH; 40°C/75% RH accelerated), aerosol performance stability, and device compatibility; lyophilised and spray-dried powders exhibit superior long-term stability compared to aqueous nanosuspensions[69,70].

Table 6: Characterization techniques and their significance for inhalable nanocarriers

Parameter	Technique	Significance	Acceptable Range
Particle Size	DLS, NTA, laser diffraction	Lung deposition efficiency	100–500 nm (aerosol: 1–5 µm MMAD)
PDI	Dynamic Light Scattering	Monodispersity indicator	< 0.3 (monodisperse)
Zeta Potential	Electrophoretic light scattering	Colloidal stability	> +30 or < -30 mV (stable)
Morphology	SEM, TEM, AFM	Shape, surface texture	Spherical preferred for inhalation
MMAD	Cascade impaction (ACI, NGI)	Aerodynamic lung deposition	1–5 µm for deep lung
Fine Particle Fraction	Next Generation Impactor	% dose reaching lower airways	> 35% (preferred)

Encapsulation Efficiency	Indirect UV-Vis / HPLC	Drug loading capacity	> 70% preferred
Drug Release	Dialysis bag, Franz cell	Release kinetics, mechanism	Biphasic or sustained profile

7. MECHANISMS OF PULMONARY TARGETING AND DRUG RELEASE:

7.1 Passive and Active Targeting

Passive targeting exploits the Enhanced Permeability and Retention (EPR) effect hyperpermeability of tumour neovascular endothelium and impaired lymphatic drainage facilitating preferential accumulation of nanoparticles (<400 nm) in pulmonary tumour tissue, demonstrated for liposomes, polymeric NPs, and micelles[71]. Alveolar macrophage (AM) targeting represents a distinct passive strategy for pulmonary TB therapy, exploiting the phagocytic nature of AMs; nanoparticles with aerodynamic diameter 1–3 µm are preferentially phagocytosed, enabling intracellular delivery to the mycobacterial-infected compartment.[81,62] Active targeting employs surface-decorated targeting ligands recognising receptors overexpressed on pathological cells: folate receptor (FR-α, overexpressed on lung adenocarcinoma) yields 3–10-fold enhanced cellular uptake for folate-conjugated nanocarriers; mannose receptor (CD206, highly expressed on AMs) targeting with mannosylated PLGA NPs achieves 3–8-fold enhanced AM uptake for selective TB drug delivery; transferrin receptor (TfR) targeting exploits elevated iron requirements of proliferating cancer cells[72,73].

7.2 Stimuli-Responsive Release and Cellular Uptake

Stimuli-responsive nanocarriers release drug cargo in response to pathological triggers: pH-responsive systems (DOPE:CHEMS lipid combinations for liposomes; poly(methacrylic acid) for polymeric systems) undergo structural transitions in the acidic milieu of inflamed tissue (pH 5.5–6.5) or phagolysosomal compartments (pH 4.5–5.5); ROS-responsive systems (thioketal, diselenide, boronate ester linkages) release drug upon oxidative activation in asthmatic, COPD, or CF airways; enzyme-responsive systems exploiting overexpressed MMP-2, MMP-9, hyaluronidase, or elastase enable selective drug activation at pathological sites. Nanocarrier uptake by pulmonary epithelial cells occurs primarily through energy-dependent endocytic pathways: clathrin-mediated endocytosis (100–200 nm, receptor-targeted systems), caveolae-mediated transcytosis (enabling transport across alveolar epithelium for systemic delivery), and macropinocytosis. AMs phagocytose particles >1 µm via Fc, complement, and scavenger receptor recognition; nanoparticles <200 nm evade phagocytosis and access non-phagocytic cell types by clathrin or caveolae-mediated endocytosis. Cationic nanocarriers exhibit enhanced uptake in both phagocytic and non-phagocytic cells due to electrostatic attraction to negatively charged cell membranes[74,75].

8. THERAPEUTIC APPLICATIONS OF INHALABLE NANOCARRIERS:

8.1 Asthma

Asthma, a chronic inflammatory airway disease characterised by reversible bronchospasm, airway hyperresponsiveness, and eosinophilic inflammation, is a primary indication for inhaled nanocarrier therapy. Inhaled corticosteroids (ICS)budesonide, fluticasone propionate,

beclomethasone dipropionate are the mainstay of asthma maintenance therapy, but conventional ICS formulations exhibit significant oropharyngeal deposition and limited action in distal small airways. PLGA nanoparticles and liposomal formulations of budesonide demonstrate sustained drug release over 24–72 hours, enabling once-daily dosing with reduced systemic adverse effects. Chitosan-coated nanoparticles exploit mucoadhesion to prolong airway drug residence; inhalable nanocarriers loaded with anti-inflammatory agents (siRNA targeting IL-4, IL-5, IL-13, TSLP) represent next-generation asthma biologics with potential for direct pulmonary delivery[76,77,78].

8.2 Chronic Obstructive Pulmonary Disease (COPD)

COPD, characterised by progressive irreversible airflow obstruction, mucus hypersecretion, and proteolytic alveolar destruction, is managed primarily with inhaled bronchodilators and ICS requiring multiple daily administrations. Nanocarrier-based sustained-release formulations of salbutamol, formoterol, and tiotropium in PLGA or chitosan nanoparticles demonstrate prolonged bronchodilation (24–48 hours) in preclinical models, suggesting potential for once-daily therapy. SLNs and NLCs loaded with antioxidants (N-acetylcysteine, curcumin, quercetin) have been explored for attenuation of ROS-mediated pulmonary damage in COPD, exploiting the ROS-rich inflammatory microenvironment for triggered drug release. Co-delivery of bronchodilator and anti-inflammatory agents in a single inhalable nanocarrier formulation represents a clinically appealing strategy for simplified COPD management[79,80,81].

8.3 Pulmonary Tuberculosis

The standard DOTS (Directly Observed Treatment, Short-course) regimen requires daily/thrice-weekly administration of 4–5 antitubercular drugs for 6–9 months, resulting in poor patient adherence and drug-resistant strain selection. Nanocarrier-mediated delivery to alveolar macrophages the primary intracellular M. tuberculosis reservoir offers enhanced intracellular drug delivery and reduced systemic toxicity[82]. PLGA nanoparticles co-encapsulating rifampicin, isoniazid, and pyrazinamide demonstrate sustained release over 7–10 days and enhanced intracellular antimycobacterial activity; in vivo guinea pig and murine TB models show significantly reduced bacterial burden compared to free drug oral administration, with potential to reduce dosing to once-weekly or biweekly[83]. Mannosylated PLGA and alginate nanoparticles achieve 3–8-fold higher intracellular drug concentrations via AM mannose receptor targeting; surface-decorated chitosan NPs with tufts in combine drug delivery with immunostimulation, synergistically enhancing anti-TB efficacy[84].

8.4 Lung Cancer

Lung cancer, comprising NSCLC (~85%) and SCLC (~15%), has the highest global cancer mortality, with over 2 million new cases annually. Inhalable nanocarrier-based chemotherapy offers direct intratumoral drug delivery at high local concentrations while minimising systemic toxicity, exploiting the EPR effect for preferential accumulation. Liposomal cisplatin and paclitaxel-loaded PEG-PLGA nanoparticles have demonstrated significantly enhanced tumour accumulation in orthotopic lung cancer models; gene therapy via inhaled lipoplexes and polyplexes delivering p53, anti-KRAS siRNA, and EGFR-targeted shRNA demonstrates tumour suppression in NSCLC animal models. CRISPR-Cas9

delivered by inhaled lipid nanoparticles (LNPs) and inhalable immunotherapy combining checkpoint inhibitors (anti-PD-1, anti-PD-L1 mRNA) with nanocarrier delivery represent cutting-edge preclinical approaches[85,86].

8.5 Pulmonary Fibrosis

IPF, characterised by progressive lung scarring driven by aberrant fibroblast activation, TGF-β signalling, and extracellular matrix deposition, has a median survival of only 2–5 years post-diagnosis; approved antifibrotic agents (pirfenidone, nintedanib) are burdened by systemic gastrointestinal adverse effects from oral administration. Inhaled nanocarrier formulations of pirfenidone and nintedanib in PLGA nanoparticles and liposomes offer direct delivery to fibroblast-rich lung parenchyma at high local concentrations, demonstrating enhanced antifibrotic efficacy in bleomycin-induced pulmonary fibrosis mouse models. Inhalable siRNA targeting TGF-β1, connective tissue growth factor (CTGF), or collagen type I delivered via polymeric or lipid nanocarriers represents a precision molecular approach to IPF therapy[87].

8.6 Cystic Fibrosis

Cystic fibrosis (CF), caused by CFTR gene mutations, is characterised by dehydrated, hyper viscoelastic airway mucus, chronic Pseudomonas aeruginosa infections, and progressive bronchiectasis; the dense mucus constitutes the primary barrier to inhaled nanocarrier delivery. PEGylated nanoparticles and "mucus-penetrating particles" (MPPs)densely PEG-coated nanoparticles (200–500 nm) with near-neutral zeta potential diffuse through CF mucus at rates approaching pure water, enabling effective drug delivery to the epithelium. Chitosan-coated NPs loaded with tobramycin or ciprofloxacin demonstrate superior antibiofilm activity against Pseudomonas aeruginosa compared to free antibiotic, attributed to enhanced penetration of biofilm polysaccharide matrix. CFTR corrector/potentiator gene therapy via inhaled LNPs represents an emerging curative approach, complementing recent CFTR modulator therapy (ivacaftor, lumacaftor, elexacaftor) success[88,89].

8.7 Pulmonary Infections and COVID-19

Inhaled nanocarrier antibiotics exploit the pharmacokinetic advantage of high local antibiotic concentrations at the infection site, potentially overcoming resistance mechanisms. Arikayce (ALIS), the first FDA-approved inhaled liposomal antibiotic (2018), enables sustained amikacin delivery within AMs for refractory Mycobacterium avium complex (MAC) lung disease; nebulised tobramycin (TOBI, TOBI Podhaler) and colistin are established treatments for Pseudomonas aeruginosa infection in CF[90]. SARS-CoV-2 primarily infects respiratory epithelium through ACE2/TMPRSS2-mediated entry, making the pulmonary mucosa the logical target for therapeutic intervention; inhaled nanocarrier delivery of antivirals (remdesivir, favipiravir, molnupiravir) has been explored to maximise local antiviral concentrations. LNP-encapsulated mRNA vaccines administered via inhalation have demonstrated robust secretory IgA and T-cell responses in the respiratory mucosa in preclinical models, with inhaled nanocarrier COVID-19 vaccines in early clinical trials[91].

8.8 Gene and Vaccine Delivery

Inhalable nanocarriers are ideally suited for pulmonary gene therapy, exploiting direct accessibility of the respiratory epithelium; siRNA targeting oncogenes (KRAS, EGFR, MYC), proinflammatory cytokines (IL-8, TNF-α), and viral replication machinery has been delivered via

cationic liposomes, polymer-lipid hybrids, and dendrimers. mRNA encoding CFTR, α1-antitrypsin, or surfactant proteins delivered via inhaled LNPs enables gene replacement therapy in genetic lung diseases; CRISPR-Cas9 RNP complexes delivered by inhaled LNPs enable precise genome editing for CFTR correction and oncogene disruption. Dry powder nano vaccines combining antigen-loaded PLGA nanoparticles with adjuvants (CpG-ODN, monophosphoryl lipid A) in inhalable microparticle vehicles represent the leading format for thermostable, needle-free respiratory immunisation, eliciting both mucosal (sIgA) and systemic (IgG, CTL) immunity[92,93].

Table 7: Inhalable nanocarriers and their therapeutic applications across respiratory diseases

Disease	Nanocarrier	Drug Payload	Key Outcome
Asthma	PLGA NPs, liposomes	Budesonide, fluticasone	Reduced systemic absorption, prolonged bronchodilation
COPD	Chitosan NPs, SLNs	Salbutamol, tiotropium	Sustained drug release, improved mucociliary penetration
Pulmonary TB	PLGA NPs, alginate NPs	Rifampicin, isoniazid, pyrazinamide	Macrophage targeting, reduced dosing frequency
Lung Cancer	Liposomes, polymeric micelles, dendrimers	Paclitaxel, docetaxel, siRNA	Tumor-specific delivery, reduced systemic toxicity
Cystic Fibrosis	Chitosan NPs, PEGylated NPs	Tobramycin, DNase	Mucus penetration, anti-biofilm activity
Pulmonary Fibrosis	Lipid NPs, polymeric NPs	Pirfenidone, nintedanib	Fibroblast targeting, reduced systemic side effects
COVID-19	LNPs, mRNA carriers	mRNA vaccines, remdesivir	Direct pulmonary immunization, mucosal immunity
Lung Infections	Liposomes (Arikayce)	Amikacin	Sustained anti-infective action, FDA-approved

10. CLINICAL TRANSLATION AND REGULATORY CONSIDERATIONS:

10.1 Clinical Trials of Inhalable Nanomedicines

The clinical translation of inhalable nanocarriers has been advancing steadily. Arikayce (ALIS) completed Phase III trials (CONVERT trial, NCT02919514) demonstrating significantly improved culture conversion rates in refractory MAC lung disease, leading to accelerated FDA approval in 2018; the subsequent ENCORE trial confirmed continued culture conversion and safety benefits[94]. Inhaled liposomal ciprofloxacin (ARD-3150, Linhaliq) was evaluated in Phase III trials for non-CF bronchiectasis with chronic Pseudomonas aeruginosa infection, demonstrating sustained time to first exacerbation. INS1009 (inhaled Treprostinil palmitil nanoparticle) progressed to Phase II for pulmonary arterial hypertension; multiple inhaled LNP-mRNA vaccines are in Phase I/II trials for COVID-19, lung cancer, and cystic fibrosis[95,96,97].

10.2 Commercially Available Inhaled Nanomedicines

TOBI Podhaler (tobramycin inhalation powder) employs PulmoSphere® porous particle technology producing low-density porous microparticles with superior aerosolization and demonstrated non-inferiority to TOBI nebuliser solution with significantly reduced treatment time and improved patient preference in Phase III trials. Pulmozyme (dornase alfa), while not a nanocarrier, represents an early inhaled biologic for CF. The clinical pipeline includes

investigational inhaled sirolimus (polymeric NPs) for lymphangioleiomyomatosis (LAM) in Phase II trials[98,99].

10.3 Regulatory Frameworks

Regulatory evaluation involves multiple intersecting guideline frameworks. In the United States, the FDA (CDER/CDRH) jointly oversees inhaled drug-device combination products; the FDA's 2018 guidance on liposomal drug products and guidance on drug products including nanomaterials provide applicable frameworks[100]. The European Medicines Agency (EMA) has published guidelines on the pharmaceutical quality of inhaled products (CPMP/QWP/049/01) covering aerodynamic particle size, device robustness, and patient studies.[76] ICH harmonised guidelinesQ8(R2) (pharmaceutical development), Q9 (quality risk management), Q10 (pharmaceutical quality systems), Q1 (stability testing)provide the overarching framework, with Quality by Design (QbD) approaches incorporating Design of Experiments (DoE) and process analytical technology (PAT) increasingly expected for novel inhalable nanocarrier products[101,102].

10.4 Manufacturing, Scale-Up, and Stability Challenges

Scale-up of inhalable nanocarrier manufacturing from laboratory to commercial scale presents substantial technical and regulatory challenges, requiring maintenance of consistent particle size distribution, drug loading, encapsulation efficiency, and batch-to-batch reproducibility[103]. The unique process sensitivity of nanoscale systems where minor changes in shear forces, temperatures, or excipient concentrations can significantly alter particle properties necessitates rigorous process understanding, risk assessment, and control strategy implementation. Physical and chemical stability of nanocarrier formulations is a critical quality attribute; aqueous nanosuspensions are prone to aggregation, Ostwald ripening, drug leakage, hydrolysis, and oxidative degradation. Lyophilised liposomes demonstrate preservation of physical properties for 2–5 years at <25°C with appropriate cryoprotectants; temperature-controlled cold chain (−80°C) is required for thermolabile mRNA LNP formulations[104,105].

Table 8: Approved and late-stage clinical inhaled nanomedicines

Product Name	Nanocarrier Type	Active Ingredient	Indication / Status
Arikayce (ALIS)	Liposome	Amikacin sulphate	MAC lung disease; FDA-approved (2018)
Pulmozyme	Inhalable protein	Dornase alfa (DNase)	Cystic fibrosis; FDA-approved
TOBI Podhaler	PulmoSphere technology	Tobramycin	Cystic fibrosis; FDA-approved
Rapamune (inhaled form)	Polymeric NPs (investigational)	Sirolimus	LAM (lymphangioleiomyomatosis); Phase II
INS1009	Prodrug nanoparticle	Treprostinil palmitil	Pulmonary arterial hypertension; Phase II
Various LNP mRNA	Lipid nanoparticle	mRNA antigen	Mucosal COVID-19 vaccine; Phase I/II

Table 9: Regulatory considerations for inhalable nanocarrier products

Regulatory Body	Guideline/ Document	Scope	Key Requirement
FDA (USA)	21 CFR 314, PQRI guidance	NDAs, ANDAs for inhalation	Bioequivalence, device characterization, in vitro-in vivo correlation
EMA (EU)	CPMP/QWP/049/01 guideline	Inhaled products, MDI/DPI	Aerodynamic particle size, device robustness, patient studies
ICH	Q8, Q9, Q10, Q1, Q3C	Pharmaceutical development, risk management	Quality by Design (QbD), stability, solvent residues
WHO	TRS 937, Annex 5	Global generic inhaled products	In vitro characterization equivalence, clinical studies waiver criteria

11. CONCLUSION AND FUTURE PERSPECTIVES:

Inhalable nanocarriers represent a scientifically compelling and clinically transformative platform for pulmonary drug delivery. By exploiting the nanoscale dimensions, tunable surface chemistry, and versatile architectural features of liposomes, polymeric nanoparticles, SLNs, NLCs, dendrimers, nanoemulsions, polymeric micelles, and hybrid nano systems, these platforms overcome the principal limitations of conventional inhaled formulation spoor lung deposition, rapid mucociliary clearance, macrophage phagocytosis, and limited drug residence time while enabling controlled drug release, active cellular targeting, and stimuli-responsive cargo delivery.

The comprehensive body of preclinical evidence across asthma, COPD, pulmonary tuberculosis, lung cancer, cystic fibrosis, pulmonary fibrosis, and COVID-19 demonstrates the remarkable therapeutic potential of inhalable nanocarriers to improve drug bioavailability, reduce dosing frequency, minimise systemic toxicity, and enable previously infeasible modalities such as pulmonary gene therapy and mucosal vaccination. The clinical validation of Arikayce and the advanced pipeline of inhaled nanomedicines in clinical trials provide important proof-of-concept for translational viability.

Significant challenges remain: development of robust and scalable manufacturing processes; characterisation of long-term pulmonary safety and nanotoxicological profiles; establishment of predictive in vitro models bridging bench to bedside; navigation of evolving regulatory frameworks for novel nanocarrier-device combinations; and demonstration of clinical superiority over established inhaled therapies in well-designed randomised controlled trials. Future directions include smart inhaler-integrated nanocarriers with digital health sensors for dose tracking, AI-assisted formulation optimisation, personalised nanomedicine leveraging pharmacogenomic profiling, and inhaled CRISPR-based gene editing for monogenic respiratory diseases. Continued interdisciplinary collaboration among pharmaceutical scientists, pulmonologists, bioengineers, and regulatory professionals will be essential to translate inhalable nanocarrier innovations into life-changing therapies for the hundreds of millions affected by respiratory diseases worldwide.

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