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Review of Novel Pulmonary Drug Delivery Systems for the Treatment of Respiratory Diseases

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Abstract: *Pulmonary drug delivery has emerged as an important strategy for the treatment of respiratory diseases because it enables drugs to be administered directly to the lungs, thereby producing high local drug concentrations while potentially reducing systemic exposure and associated adverse effects. Conventional inhalation systems, including pressurized metered-dose inhalers, dry powder inhalers, nebulizers, and soft-mist inhalers, have become fundamental technologies for the management of asthma and chronic obstructive pulmonary disease. However, limitations related to drug deposition, patient inhalation technique, formulation stability, mucociliary clearance, macrophage uptake, and variability in pulmonary delivery have encouraged the development of novel delivery platforms.*

Keywords: Pulmonary drug delivery, inhalation, dry powder inhaler, nanoparticles, microparticles, liposomes, respiratory diseases, targeted drug delivery

I. INTRODUCTION

Respiratory diseases represent an important therapeutic challenge because conventional systemic administration may result in inadequate drug concentrations at the pulmonary site while simultaneously increasing systemic exposure. Pulmonary administration provides a direct route to the respiratory tract and takes advantage of the extensive surface area, relatively thin epithelial barrier, and rich vascularization of the lungs. Consequently, inhaled therapy can provide rapid local action and, for appropriately designed molecules, reduced systemic adverse effects.

These characteristics have made pulmonary delivery particularly important in asthma, COPD, pulmonary infections, cystic fibrosis, pulmonary hypertension, and other respiratory disorders. Reviews published during the study period have emphasized that pulmonary delivery can provide both local and systemic therapeutic effects, although successful delivery depends strongly on particle characteristics, formulation properties, aerosolization, device design, and patient inhalation behavior (Mehta, 2016; Chow et al., 2023).

The conventional pulmonary delivery landscape includes pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), nebulizers, and soft-mist inhalers. Although these systems are clinically established, their performance can be influenced by coordination requirements, inspiratory flow rate, device resistance, formulation characteristics, and patient technique. In particular, DPI performance depends on the interaction among powder formulation, inhaler geometry, aerosolization, deagglomeration, and the patient's inspiratory profile. Therefore, achieving reproducible deep-lung deposition remains an important technological challenge (Islam & Cleary, 2012).

The development of novel pulmonary delivery systems has attempted to overcome these limitations by manipulating particle size, morphology, surface properties, density, porosity, drug loading, release characteristics, and targeting mechanisms. Nanotechnology has provided opportunities for the development of inhalable nanoparticles and nanoparticle-containing microparticles, while particle engineering has facilitated the preparation of powders with improved dispersibility and aerodynamic behavior. Inhalable nanoparticulate powders have attracted considerable interest because they can potentially improve drug targeting and therapeutic performance when appropriately engineered for pulmonary deposition (Mansour et al., 2015).

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PHYSIOLOGICAL BASIS OF PULMONARY DRUG DELIVERY

The respiratory tract provides a large surface for drug deposition and absorption. However, the lungs possess several defense mechanisms that can limit drug residence time. Mucociliary clearance can remove deposited material from conducting airways, while alveolar macrophages can recognize and internalize particulate materials reaching the deeper lung. Particle aerodynamic diameter therefore plays a major role in determining where an inhaled formulation deposits. Dry-powder reviews have emphasized that aerodynamic properties, particle morphology, density, hygroscopicity, cohesion, and dispersion characteristics collectively influence aerosolization and deposition (Feinberg et al., 2020).

For pulmonary delivery, formulation particles generally need appropriate aerodynamic characteristics to reach the desired regions of the respiratory tract. Particles that are too large may predominantly deposit in the upper airways, whereas appropriately engineered particles can reach smaller bronchioles and alveolar regions. The objective is not simply to reduce particle size to the nanoscale; instead, formulation scientists must balance aerodynamic behavior with powder flow, dispersibility, stability, drug loading, and clearance. This has encouraged the development of microparticles containing nanoparticles, large porous particles, and other engineered structures capable of achieving favorable aerodynamic properties while retaining nanoscale drug-delivery functions.

CONVENTIONAL PULMONARY DELIVERY SYSTEMS AND THEIR LIMITATIONS

pMDIs remain an established inhalation platform, particularly for bronchodilators and corticosteroids. They can provide accurate metered doses but may require appropriate coordination between actuation and inhalation. DPIs eliminate the need for propellants and can be relatively portable and stable, but their performance depends substantially on the patient's inspiratory effort and the powder's ability to disperse. Nebulizers can be useful when patients cannot effectively use handheld inhalers, although they can be comparatively less portable and may require longer administration times. Soft-mist inhalers generate a slowly moving aerosol and provide another approach to improving inhalation performance.

The selection of an inhaler should therefore consider both the formulation and patient characteristics. A 2023 review of inhaled therapy for asthma and COPD emphasized that device selection and patient-specific requirements are important determinants of effective inhaled treatment, while emerging biologic therapies present additional challenges for pulmonary delivery (Chow et al., 2023).

DRY POWDER INHALERS AS NOVEL PULMONARY PLATFORMS

Dry powder inhalers have undergone considerable technological development during 2010–2023. Unlike pMDIs, they generally do not require a propellant and can offer favorable stability and portability. However, the formulation must be engineered so that drug particles can efficiently detach from one another or from carrier particles during inhalation. The resulting aerosol should possess adequate fine-particle characteristics for deposition in the target lung region.

Research has therefore investigated carrier-free powders, engineered carrier systems, spray-dried particles, porous particles, and nanoparticle-containing powders. Powder engineering techniques include milling, spray drying, spray-freeze drying, supercritical-fluid processing, thin-film freezing, and other specialized methods. These approaches can modify particle morphology and improve aerosolization and deposition (Feinberg et al., 2020).

The continuing evolution of DPIs has also focused on device–formulation interactions. The inhaler must generate sufficient energy to deagglomerate the powder without compromising dose consistency. Consequently, DPI development involves pharmaceutical formulation, aerosol physics, device engineering, powder mechanics, and patient factors. The complexity of these interactions was identified as a major obstacle to achieving consistently reliable pulmonary dosing (Islam & Cleary, 2012).

POLYMERIC MICROPARTICLES

Polymeric microparticles are among the important novel approaches to pulmonary drug delivery. Biodegradable polymers can be used to encapsulate drugs and provide controlled or sustained release. Such systems may increase

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pulmonary residence time and reduce the frequency of administration. Depending on their composition and surface characteristics, polymeric particles may also be designed to interact with specific cells or pulmonary structures.

Inhalable microparticles based on polysaccharides, lipids, proteins, and synthetic or natural polymers have been investigated extensively. Their performance is affected by drug loading, particle morphology, aerodynamic size, release behavior, cytocompatibility, and interactions with lung fluids. A 2022 review published in *Regenerative Biomaterials* highlighted the continuing development of inhalable microparticles for dry-powder formulations and emphasized their potential for controlled release and specialized therapeutic applications (Knap et al., 2022).

NANOPARTICLE-BASED PULMONARY DRUG DELIVERY

Nanoparticles have attracted significant attention because their small size and modifiable surface can facilitate novel drug-delivery strategies. Polymeric nanoparticles, lipid nanoparticles, nanocrystals, and other nanosystems can potentially improve the solubility, stability, retention, and controlled release of poorly water-soluble or unstable therapeutic compounds.

However, directly aerosolizing nanoparticles creates an important engineering problem: nanoparticles may possess unfavorable flow and aerosolization characteristics because of strong interparticle interactions. One solution is to incorporate nanoparticles into larger microparticles that have suitable aerodynamic properties. After deposition in the lung, the microparticles may disperse or dissolve and release the nanoparticles. This strategy is commonly referred to as a nano-in-microparticle approach.

Reviews have described inhalable nanoparticulate powders as a promising platform for targeted pulmonary delivery, particularly when particle engineering is used to achieve appropriate aerosol characteristics (Mansour et al., 2015). Nevertheless, a 2023 review noted an important translational gap: despite extensive research into nanoparticle-based dry-powder formulations, such systems had not yet achieved broad regulatory approval, highlighting challenges between laboratory development and clinical implementation.

LIPOSOMAL PULMONARY DELIVERY

Liposomes are vesicular carriers composed primarily of phospholipid bilayers. Their ability to encapsulate hydrophilic and lipophilic compounds makes them attractive for pulmonary delivery. Liposomes can potentially protect drugs from degradation, modify release profiles, and alter drug distribution within pulmonary tissues.

Inhaled liposomal formulations have been investigated for antimicrobial, anti-inflammatory, anticancer, and other therapeutic applications. The composition, surface charge, vesicle size, lipid stability, encapsulation efficiency, and aerosolization characteristics all influence their performance. Pulmonary administration may also reduce systemic exposure when a drug is intended to act locally in the lungs.

A major challenge is maintaining liposomal integrity during formulation processing and aerosolization. Therefore, specialized powder-production approaches such as spray drying or spray-freeze drying may be employed to convert liquid vesicles into inhalable dry formulations while attempting to preserve their functional characteristics.

SOLID LIPID NANOPARTICLES AND LIPID-BASED SYSTEMS

Solid lipid nanoparticles provide another lipid-based platform for pulmonary delivery. These systems can encapsulate lipophilic drugs and may provide controlled release and improved drug stability. Their lipid composition can be modified to influence particle characteristics and drug-release behavior.

Lipid-based particles are particularly attractive for drugs requiring improved solubility or protection from degradation. However, pulmonary safety and long-term effects must be carefully considered because the lung has specialized defense mechanisms and relatively limited tolerance for certain materials. Thus, physicochemical characterization must be accompanied by appropriate biological and toxicological evaluation.

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NANOCRYSTALS AND POORLY SOLUBLE DRUGS

Many pharmaceutical compounds have poor aqueous solubility, which can restrict their performance after inhalation. Drug nanocrystals can increase effective surface area and thereby improve dissolution. For pulmonary delivery, nanocrystals can be incorporated into inhalable powders or other formulations.

The main advantage of this approach is that the carrier burden may be relatively low because the drug itself constitutes the major particulate component. Nevertheless, stabilization against aggregation and achievement of suitable aerosol properties remain important formulation challenges. Novel powder-engineering techniques have therefore become increasingly important in developing inhalable nanocrystal formulations.

LARGE POROUS PARTICLES AND ENGINEERED PARTICULATE SYSTEMS

Large porous particles represent an important strategy for improving pulmonary deposition while maintaining a relatively large geometric particle size. Because aerodynamic behavior depends on both size and density, highly porous particles can have a relatively large geometric diameter while maintaining an aerodynamic diameter suitable for pulmonary delivery. Their larger structure may also reduce some forms of rapid clearance.

Other engineered systems include swellable microparticles, composite particles, nano-in-microparticles, and effervescent particles. These systems demonstrate a shift from simple micronization toward sophisticated particle engineering. The objective is to simultaneously control aerodynamic performance, drug loading, dispersion, deposition, release, and biological interaction.

SPRAY-DRIED AND SPRAY-FREEZE-DRIED PULMONARY FORMULATIONS

Spray drying has become one of the most widely used techniques for preparing inhalable powders. It permits manipulation of particle size, morphology, density, composition, and moisture content. Spray-dried powders can incorporate drugs with polymers, lipids, proteins, sugars, and other excipients.

Spray-freeze drying provides an alternative approach that can produce highly porous particles with potentially favorable aerosol properties. These technologies are especially relevant for sensitive biological molecules because formulation conditions can be adapted to improve stability. Reviews of dry powders have identified spray drying and spray-freeze drying among the important techniques for producing inhalable formulations with tailored physicochemical properties (Feinberg et al., 2020).

PULMONARY DELIVERY OF BIOLOGICS, PROTEINS, PEPTIDES AND NUCLEIC ACIDS

Pulmonary delivery is increasingly being investigated for molecules that are difficult to administer using conventional oral routes, including proteins, peptides, nucleic acids, and other biological therapeutics. Direct delivery to the lung may potentially reduce systemic exposure and facilitate local activity.

Nevertheless, biological molecules may be sensitive to aggregation, enzymatic degradation, shear stress, temperature, moisture, and processing conditions. Their formulation into stable inhalable powders is therefore considerably more challenging than conventional small-molecule formulation. Current research emphasizes the importance of multidisciplinary approaches combining molecular design, formulation science, particle engineering, device development, and biological evaluation (Bermudez et al., 2021).

COMPARATIVE OVERVIEW OF NOVEL PULMONARY DRUG DELIVERY SYSTEMS

Delivery system	Major characteristics	Potential advantages	Important limitations	Representative applications
Dry powder inhalers	Solid micronized/engineered powders	Propellant-free, portable, good stability	Dependent on inspiratory flow and powder dispersion	Asthma, COPD

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Polymeric microparticles	Biodegradable polymer carriers	Controlled release, increased residence time	Manufacturing complexity and safety evaluation	Asthma, infection, cancer
Nanoparticles	Nano-sized drug/carrier systems	Targeting, controlled release, improved solubility	Aggregation, aerosolization, translational challenges	Infection, cancer, inflammatory diseases
Liposomes	Phospholipid vesicles	Encapsulation of hydrophilic/lipophilic drugs	Stability and aerosolization challenges	Infection, inflammation, cancer
Solid lipid nanoparticles	Lipid-based nanocarriers	Drug protection and controlled release	Physical stability and pulmonary safety	Anti-inflammatory and antimicrobial therapy
Nanocrystals	Drug crystals at nanoscale	Enhanced dissolution of poorly soluble drugs	Stabilization and aerosol engineering	Poorly soluble drugs
Large porous particles	Low-density engineered particles	Favorable aerodynamic properties	Complex manufacturing	Deep-lung delivery
Nano-in-microparticles	Nanoparticles incorporated into microparticles	Combines nanoscale function with inhalable aerodynamic size	Multistep formulation	Targeted pulmonary delivery
Spray-dried powders	Engineered particles produced by spray drying	Adjustable size, morphology and composition	Process optimization required	Asthma, COPD, infection
Spray-freeze-dried powders	Highly porous particles	Potentially favorable dispersibility	Higher process complexity	Sensitive drugs/biologics
Smart/advanced inhalers	Device–formulation integration	Improved dose delivery and usability	Cost and device complexity	Chronic respiratory disease

The development of these systems demonstrates that novel pulmonary delivery is moving from simple aerosol generation toward integrated formulation–device engineering. Reviews published during 2010–2023 consistently identify particle engineering, aerosolization, device design, and patient use as interconnected determinants of therapeutic performance (Islam & Cleary, 2012; Mehta, 2016; Chow et al., 2023).

II. CONCLUSION

The literature published between 2010 and 2023 demonstrates substantial development in pulmonary drug delivery technology. Conventional pMDIs, DPIs, nebulizers, and soft-mist inhalers have provided the foundation for respiratory pharmacotherapy, while newer approaches have attempted to overcome limitations in deposition, release, stability, targeting, and patient usability. Polymeric microparticles, nanoparticles, liposomes, solid lipid nanoparticles,

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nanocrystals, large porous particles, nano-in-microparticles, spray-dried powders, and spray-freeze-dried formulations represent important directions in modern pulmonary drug delivery.

Among these, particle engineering and nanoparticle-based dry powders have received considerable attention because they can potentially combine targeted drug delivery with favorable aerosol properties. Nevertheless, laboratory success does not necessarily guarantee clinical applicability. Challenges associated with aerosolization, pulmonary clearance, formulation stability, scale-up, toxicity, regulatory requirements, and patient variability remain significant. Overall, the evidence from 2010–2023 supports continued investigation of novel pulmonary systems, particularly through multidisciplinary approaches that integrate pharmaceutical formulation, nanotechnology, aerosol science, device engineering, and clinical research.

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