Review Article

# Engineering the Future of Pulmonary Drug Delivery: Next-Generation Dry Powder Inhalers from Advanced Particle Design to Smart Therapeutic Systems

**Mattam Jyothika[1,2] K. Sudhamani [1*] R.Prasanthi [1]**

[1*]Department of Pharmaceutics, Malla Reddy Institute of Pharmaceutical sciences, Malla Reddy Vishwa vidyapeeth, Hyderabad, Telangana-500055, India.

[2] Research Associate, Austrak Pvt Limited, Austrak house, West Marredpally,500026

**Corresponding author****

K. Sudhamani

Department of Pharmaceutics, Malla Reddy Institute of Pharmaceutical sciences,

Malla Reddy Vishwavidyapeeth, (Deemed to be University), Suraram,

Hyderabad 500055 Telangana, India.

E-mail address: sudhamanikotturu@gmail.com

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**Abstract**

Dry powder inhalers (DPIs) are increasingly sophisticated pulmonary drug-delivery platforms in which formulation properties, particle engineering, device design, inspiratory airflow and patient factors jointly determine therapeutic performance. Their propellant-free operation, portability and capacity for local delivery have established DPIs in respiratory medicine, while advances in spray drying, spray freeze-drying, thin-film freezing, nano-in-micro systems and biologic stabilization are broadening their potential applications. Recent research also emphasizes computational fluid dynamics, human-factors engineering, connected inhalers and environmentally sustainable design. This critical review integrates fundamental principles with recent developments in DPI formulation, manufacture, aerosolization, lung deposition, evaluation and therapeutic application. Particular attention is given to the limitations of current technologies, the gap between promising laboratory formulations and clinical translation, and the need for stronger formulation–device–patient integration. Future progress will depend on scalable manufacturing, clinically relevant aerosol testing, robust in vitro–in vivo relationships, improved delivery for patients with limited inspiratory capacity and evidence-based implementation of digital and computational technologies [1–8].

Keywords **.**Dry powder inhaler; pulmonary drug delivery; particle engineering; aerosolization; nanocarrier; spray drying; biologics; computational fluid dynamics; smart inhaler.

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## 1. Introduction

Pulmonary drug delivery offers direct access to the respiratory tract and can provide rapid local action while limiting systemic exposure. The large epithelial surface, extensive vascularization and short diffusion distance of the distal lung also make pulmonary administration attractive for selected systemic therapies. However, the respiratory tract is a highly efficient biological filter; airway geometry, mucociliary clearance, alveolar macrophages, breathing patterns and disease-associated changes can restrict deposition and retention [1,9–12].

DPIs deliver solid drug particles using energy derived primarily from the patient's inspiratory maneuver. Unlike pressurized metered-dose inhalers, they generally do not require a propellant. Their apparent simplicity conceals a complex product in which formulation, device and patient are inseparable determinants of performance. Fine particles suitable for lung delivery are highly cohesive, making reproducible metering, fluidization and deagglomeration difficult. Consequently, DPI development requires expertise in aerosol science, powder technology, pharmaceutical engineering, device design and clinical use [1–4,13].

The field has progressed beyond conventional micronized drug–lactose blends. Contemporary strategies include engineered porous particles, surface modification, nano-in-micro systems,

lipid and polymeric carriers, biologic powders, computationally optimized devices and connected inhalers [4–8,14–18]. Nevertheless, clinical translation remains substantially slower than the volume of preclinical research suggests. This review therefore combines a broad overview of DPI science with critical analysis of recent advances, translational barriers and future research priorities.

## 2. Respiratory Anatomy, Barriers and Particle Deposition

The respiratory tract can be divided into conducting and respiratory regions. The conducting airways transport, warm, humidify and filter inspired air. The respiratory region comprises respiratory bronchioles, alveolar ducts and alveoli and provides a large surface for gas exchange and drug absorption [9–11].

Three principal mechanisms govern aerosol deposition: inertial impaction, gravitational sedimentation and Brownian diffusion. Impaction is prominent for larger particles and at sites of abrupt airflow change; sedimentation becomes important in smaller airways under low flow conditions; diffusion predominantly affects ultrafine particles. Aerodynamic diameter, rather than geometric diameter alone, is a key determinant because it incorporates particle size, density and shape. Particles in the respirable range can access the lower airways, although actual deposition varies with formulation, device, inhalation profile and patient anatomy [1,10–12].

A major limitation of simplified particle-size rules is that they can obscure patient-specific variability. Mouth–throat geometry, inspiratory acceleration, airway obstruction and disease severity can substantially alter deposition. Therefore, next-generation DPI development should combine conventional aerodynamic testing with realistic airway models, computational simulations and, where appropriate, clinical deposition studies [3,19–22].

## 3. Components and Classification of DPI Systems

A DPI product generally comprises an active pharmaceutical ingredient (API), optional carrier particles, functional excipients, packaging and an inhaler device. Micronized APIs exhibit high surface area and strong cohesive and adhesive interactions. Coarse carriers, most commonly lactose, can improve flow, metering and content uniformity, but efficient delivery requires drug detachment during inhalation [2,23–26].

Functional excipients may modify particle surfaces, stabilize proteins, reduce moisture sensitivity or improve dispersibility. Leucine, phospholipids, sugars and selected polymers have been investigated for these purposes. Excipients must be selected according to safety, route-specific acceptability, processing conditions and the intended product profile [5,27–29].

Devices are commonly classified as single-dose, multi-unit-dose and reservoir DPIs. Single-dose devices require loading of a capsule or unit dose. Multi-unit systems contain individually protected doses, while reservoir devices meter powder from bulk storage. These designs differ in dose protection, convenience, complexity and sensitivity to handling. Device resistance is particularly important because it influences the pressure drop and airflow generated by the patient [2–4,30].

## 4. Mechanism of Powder Aerosolization and Lung Delivery

After dose preparation, inspiratory airflow enters the inhaler and provides energy for powder fluidization and dispersion. Turbulence, shear, particle–particle collisions and particle–device impacts contribute to deagglomeration. In carrier-based formulations, drug particles must detach from carrier surfaces while avoiding excessive deposition inside the device or oropharynx [2,3,23].

The traditional assumption that higher airflow always improves delivery is incomplete. Stronger airflow can enhance deagglomeration but may also increase throat deposition. Optimal performance therefore depends on balancing device resistance, turbulence generation, formulation properties and patient capability. This interaction explains why a formulation cannot be meaningfully optimized independently of its delivery device [3,4,19].

## 5. Formulation Strategies

Carrier-based blends remain commercially important because they improve handling of low-dose cohesive powders. Their performance is influenced by carrier size, morphology, surface roughness, fines content, moisture, mixing conditions and drug–carrier adhesion. Although lactose is dominant, alternative sugars and other carriers have been investigated [23–26].

Carrier-free systems use engineered drug-containing particles with controlled morphology, density and surface characteristics. These approaches may reduce some limitations of drug–carrier detachment and allow higher drug loading, but they introduce challenges in manufacture, physical stability and dose metering [1,13,31].

The choice between carrier-based and carrier-free systems should not be framed as a universal superiority question. Carrier-based systems offer established manufacturing experience, whereas

engineered particles can provide greater control of aerosol properties and accommodate complex molecules. Selection should be driven by dose, drug properties, stability, device design, patient population and commercial scalability.

| Strategy | Main advantage | Key limitation | Research priority |
|---|---|---|---|
| Carrier-based blends | Established processing and dose handling | Drug–carrier adhesion and variable detachment | Control surface properties and patient-flow dependence |
| Carrier-free engineered particles | High drug loading and tunable aerosol properties | Manufacturing and stability complexity | Scalable robust particle engineering |
| Nano-in-micro systems | Potential targeting and modified release | Complexity, safety and translation gap | long-term safety and industrial scale-up |
| Biologic dry powders | Potential improved storage and non-invasive delivery | Loss of biological activity | Stabilization and clinically relevant dosing |

**Table 1** compares the major formulation strategies used in DPI development, emphasizing their principal benefits, limitations and research priorities. The comparison shows that no single approach is universally optimal; formulation selection should consider aerosol performance, stability, manufacturability and patient requirements. Further work should prioritize reproducible particle engineering and clinically relevant performance.

**6. Particle Engineering and Manufacturing Technologies**

Jet milling is widely used to produce micronized particles but may generate irregular morphology, amorphous regions and high surface energy. Spray drying provides greater control over size, density, morphology and composition and is therefore central to modern DPI research [1,13,31–34].

Spray freeze-drying can generate highly porous particles under relatively mild thermal conditions, although long processing times, cost and scale-up remain concerns. Thin-film freezing has attracted interest for producing brittle matrix powders with high surface area and favorable aerosol performance. Supercritical-fluid methods and other emerging techniques provide additional routes for particle design but require careful evaluation of reproducibility, solvent removal and industrial feasibility [1,31–36].

A persistent weakness in the literature is the emphasis on excellent laboratory aerosol metrics without equivalent attention to process robustness. A technology that produces a high fine-particle fraction at small scale may still fail because of yield, batch variability, storage instability or device incompatibility. Future studies should incorporate quality-by-design principles and manufacturability earlier in development [37–39].

**7. Evaluation and Quality Assessment**

Physicochemical characterization commonly includes particle-size distribution, morphology, density, surface properties, crystallinity, moisture content, flow behavior, drug content and stability. Aerodynamic performance is evaluated using emitted dose, fine-particle dose, fine-particle fraction, mass median aerodynamic diameter and geometric standard deviation [1,40–42].

Cascade impactors, particularly the Next Generation Impactor, are widely used for aerodynamic assessment. However, compendial testing conditions do not fully reproduce patient inhalation profiles or airway anatomy. More clinically relevant methods include realistic mouth–throat models, breathing simulators and computational approaches [19–22,40].

The development of reliable in vitro–in vivo correlations remains difficult because clinical

deposition depends on multiple interacting variables. Better integration of aerosol measurements, imaging, pharmacokinetics and patient-specific modelling could improve predictive development.

**8. Therapeutic Applications**

DPIs are established for bronchodilators, corticosteroids and combination therapies in asthma and chronic obstructive pulmonary disease. Research applications include inhaled antibiotics, antifungals, vaccines, anticancer agents and therapies for systemic delivery [1,5,43–45].

Pulmonary administration of high-dose anti-infective agents is attractive because high local concentrations may be achieved while reducing systemic exposure. Nevertheless, high powder mass creates challenges for dose delivery, tolerability and inhalation burden. Similarly, pulmonary delivery of anticancer drugs may improve local exposure but requires careful evaluation of toxicity, distribution and clearance.

The expanding therapeutic scope of DPIs should be assessed critically. Demonstration of aerosol performance is only an early step; successful translation requires disease-relevant efficacy, toxicology, scalable production, device compatibility and patient acceptability.

**9. Nano-in-Micro and Nanocarrier-Based DPIs**

Nanoparticles, liposomes, lipid carriers and polymeric systems can provide drug protection, modified release and cellular targeting. Because isolated nanoparticles often aerosolize poorly, nano-in-micro strategies embed nanoscale carriers in respirable microparticles that disperse during inhalation and release the nanocarrier after deposition [6,7,14–18].

Despite extensive preclinical research, translation of nanoparticle-based DPI products remains limited. Challenges include nanoparticle stability during drying, redispersibility, residual solvents, manufacturing complexity, dose reproducibility, long-term pulmonary safety and regulatory characterization. The absence of widespread approved nano-DPI products demonstrates the gap between formulation novelty and clinical feasibility [16].

Future research should compare advanced systems against clinically meaningful controls rather than only demonstrating superiority to unoptimized formulations. Long-term toxicology and scalable manufacturing deserve equal emphasis with aerosol performance.

**10. Pulmonary Delivery of Biologics and Nucleic Acids**

Proteins, peptides and nucleic acids are increasingly investigated for pulmonary delivery. Dry powders may improve storage stability compared with some liquid systems, but processing can cause aggregation, denaturation or loss of biological activity [5,32,46–48].

Spray drying and related technologies require optimization of temperature exposure, interfacial stress and excipient selection. Sugars, amino acids and other stabilizers can protect macromolecules, but the formulation must retain both biological activity and aerosol performance. For nucleic-acid therapeutics, additional challenges include intracellular delivery, nuclease protection and endosomal escape [5,46–48].

The future of inhaled biologics will depend on moving beyond proof-of-concept powders toward reproducible manufacturing, long-term stability and clinically relevant dosing.

**11. Computational Modelling and Artificial Intelligence**

Computational fluid dynamics (CFD) is used to study airflow, turbulence and particle transport within DPI devices and respiratory airways. Discrete element methods can model particle interactions, while coupled CFD–DEM approaches offer a more detailed representation of powder behavior [3,8,49,50].

Computational methods can reduce experimental screening and reveal mechanisms that are difficult to measure directly. However, predictive accuracy depends on assumptions, boundary conditions, turbulence models and experimental validation. Models should therefore complement rather than replace physical testing [8,49,50].

Artificial intelligence and machine learning may assist formulation optimization, pattern recognition and patient-specific prediction. At present, claims regarding AI-enabled personalized DPI therapy are ahead of robust clinical evidence. High-quality datasets, interpretability, external validation and regulatory clarity are required before routine implementation.

**12. Smart Inhalers and Human-Factors Engineering**

Connected inhalers can record device use, provide reminders and support adherence monitoring. Their potential value lies not merely in collecting data but in converting reliable information into interventions that improve outcomes. Data accuracy, interoperability, privacy, cost and sustained patient engagement remain important challenges.

Human-factors engineering aims to reduce critical use errors by considering patient capabilities throughout device development. Device simplicity, feedback, loading procedures, inspiratory requirements and instructions can

influence successful use. Recent work emphasizes that improvements in formulation should be accompanied by patient-centered device design [4,30].

**13. Sustainability**

DPIs are propellant-free and can have environmental advantages compared with some propellant-based inhalers. Nevertheless, sustainability assessment should consider the full product lifecycle, including materials, manufacturing, packaging, transportation and disposal. Reusable devices and recyclable materials may reduce environmental burden, but environmental benefits should be evaluated alongside safety, adherence and therapeutic effectiveness.

| Advance | Potential contribution | Remaining challenge |
|---|---|---|
| Advanced spray drying | Control of morphology and composition | Scale-up and process-induced instability |
| Thin-film freezing | Highly porous, dispersible powders | Industrial implementation |
| CFD/DEM modelling | Mechanistic device optimization | Validation and computational assumptions |
| Smart inhalers | Adherence monitoring and feedback | Cost, privacy and clinical integration |
| AI/ML | Optimization and prediction | Dataset quality and external validation |
| Sustainable design | Reduced lifecycle environmental burden | Balancing sustainability with usability and cost |

**Table 2** summarizes selected recent advances in DPI technology together with the major barriers that may affect their translation into practical products. Current progress is increasingly focused on engineered particles, computational modelling, digital inhalers and sustainable design. Nevertheless, scale-up, validation, cost, safety and clinical integration remain key priorities.

**14. Emerging Potential in Inflammatory and Autoimmune-Associated Pulmonary Disease**

Targeted pulmonary delivery may offer opportunities in inflammatory and autoimmune-associated lung diseases by increasing local drug exposure while potentially reducing systemic toxicity. This concept is relevant to diseases in which inflammation and fibrosis coexist and conventional systemic therapy is limited by adverse effects.

However, translation requires disease-specific understanding of altered airway anatomy, mucus, inflammation, fibrosis and clearance. For inhaled disease-modifying agents, studies must establish local efficacy, pulmonary safety, pharmacokinetics and the relationship between regional deposition and therapeutic response. This remains a promising but comparatively underdeveloped area for DPI research.

**15. Critical Challenges and Research Gaps**

The central challenge in DPI development is integration. Formulation, device and patient factors are often studied separately even though clinical performance emerges from their interaction. Another major gap is the weak translation of sophisticated preclinical formulations into approved products.

Research priorities include standardized reporting of aerosol performance, realistic patient-relevant testing, long-term safety of novel excipients and nanocarriers, scalable manufacturing, robust stability studies, improved delivery for patients with limited inspiratory capacity and better in vitro–in vivo relationships. Comparative studies should use meaningful benchmarks and clinically relevant endpoints.

Regulatory science must also evolve alongside complex formulations and digital systems. Developers should consider quality, manufacturability and regulatory expectations from the earliest stages rather than treating them as late-stage concerns.

**16. Future Perspectives**

Future DPI development will increasingly combine precision particle engineering, biologic stabilization, computational modelling, digital monitoring and patient-centered device design. The most successful technologies are unlikely to be those with the most complex formulation, but those that achieve a practical balance of efficacy, stability, usability, manufacturability and cost.

Digital and AI technologies may support personalization, but their value must be demonstrated through clinically meaningful outcomes. Advanced nanocarriers and biologics will require stronger translational evidence.

Sustainability will become an increasingly important design consideration.

A major opportunity lies in developing integrated platforms in which formulation properties, device airflow and patient physiology are optimized together. Such an approach could reduce variability and accelerate translation from laboratory research to effective therapy.

**17. Conclusion**

Dry powder inhalers have evolved into versatile pulmonary drug-delivery platforms. Their performance is governed by complex interactions among particle properties, formulation composition, device engineering, inspiratory behavior and respiratory physiology. Recent advances in engineered particles, nano-in-micro systems, biologics, computational modelling and connected devices are broadening therapeutic possibilities.

Nevertheless, technological novelty alone does not guarantee clinical success. The field must address manufacturing scalability, stability, patient variability, realistic testing, long-term safety and regulatory translation. Future progress will depend on multidisciplinary development strategies that treat the formulation, device and patient as a single integrated system.

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