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**Inhalation beyond respiratory: the surprising applications of dry powder inhalers**

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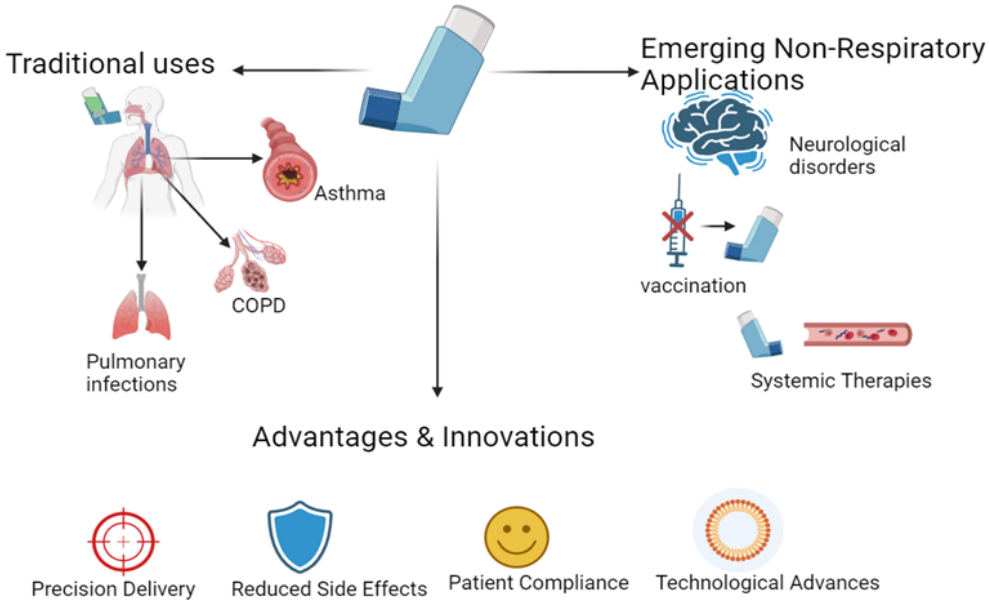
**Abstract**

Dry powder inhalers (DPIs) are the newer devices whereby medicine is dispensed as a fine powder inhaled deeply into the lungs, which is more simplified and stable compared to the pressurized metered dose inhalers. DPIs were developed primarily for respiratory disorders such as asthma and chronic obstructive pulmonary disease but are being investigated for other uses. This review explicates the features of DPIs and how they are made, looking at their effectiveness in respiratory therapy, noting features such as usability, stability of the drugs, and flexibility. It also discusses the potential of systemic drug delivery using other routes, such as insulin for diabetes, calcitonin for osteoporosis, antibacterial agents, vaccines, dermal treatments, and ocular treatments, considering issues like stability and patients' compliance. Issues related to jet milling, spray drying, and supercritical fluid technology are also covered with regard to improving DPI performance. Hindrances, including formulation stability and regulatory issues, have been discussed as a way of demonstrating how innovation is needed to go beyond respiratory therapy.




**Graphical abstract**

**Key words**: DPI, particle size, respiratory drugs, inhalers, asthma, COPD.

## Introduction

Dry powder inhalers [DPIs] are devices designed to deliver dry powdered medication directly to the lungs, providing an alternative to inhalers that use propellants or liquid formulations [1]. The overview of DPI is depicted in Figure 1. DPIs are favoured for their portability, ease of use, and effectiveness in delivering respiratory drugs [2]. Pulmonary drug delivery has several advantages, including minimizing first-pass metabolism, enhancing drug deposition in the lungs, and reducing systemic toxicity [3]. This method is beneficial for treating respiratory disorders such as asthma, COPD, and pneumonia. DPIs, along with breath-actuated nebulizers, meter dose inhalers [MDIs], and soft mist inhalers [SMIs], are the most commonly used devices for pulmonary medication administration. Unlike nebulizers and MDIs, DPIs do not require propellants and offer better chemical stability and ease of transport [4]. Advances in particle and device technology, such as spray-drying and freeze-drying, have improved DPI systems' performance. Despite these advancements, the solid-state characteristics and physical stability of DPI formulations are often overlooked in the literature, even though they significantly impact the inhalation product's quality and performance [5].

### *Mechanism of action*

DPIs work by distributing and supplying the powdered drug into the respiratory system through the patient's inhaling effort. The mechanism of DPI is illustrated in Figure 2. The patient's inhalation usually initiates activation, which makes sure the drug is delivered at the appropriate time [6].

### *Powder formulation*

In DPIs, the medications are prepared as dry powders that have been finely ground [7]. The powder's ideal particle size is intended to allow for deep lung penetration and effective drug absorption [8]. The various methods of powder production for DPI are shown in Figure 3.

- Jet milling

  Micronization, crucial for creating respiratory particle sizes for Dry Powder Inhalers [DPIs], involves reducing particle size to micrometers using mechanical energy [9]. Jet milling, a common pharmaceutical method, employs compressed gas for particle size reduction. Types include full impact, opposed-jet, and spiral-jet mills [10]. While cost-effective and producing inhalable particles, jet milling can cause agglomeration due to increased surface energy and electrostatic charge [11]. It also raises energy consumption and amorphous content, affecting stability and fine particle fraction [12]. Techniques like isothermal microcalorimetry and dynamic water vapor sorption [DVS] assess amorphous content in micronized samples [13].

- Spray drying

  Spray drying is one of the most widely utilized techniques for particle engineering to develop fine particles for inhalation purpose. In this method, a feed solution or suspension is sprayed into a hot drying medium [air/nitrogen gas] in a manner that is intended to produce particles. The distinguished feature of this technology is the ability to direct and modify the properties of the particles like size, density, shape and composition of the surface by altering the formulation or process factors. Also, in this one-step continuous manufacturing process, it is possible to have more than one component in the same particle. This method is being increasingly used by the pharmaceutical industry to produce dry powders for inhalation in the range of sizes of 1–5 μm [14].

- Spray freeze drying

  Spray freeze-drying [SFD] effectively dries heat-sensitive molecules, producing porous particles with large surface areas ideal for inhalation. Unlike traditional lyophilization, SFD customizes particle size, surface area, and density [15]. The process includes freezing the feedstock into ice and sublimating it to obtain powder, ensuring biopharmaceutical stability at low temperatures [16]. This results in light, porous particles that retain therapeutic viability and structure [17]. SFD has been used for bio-aerosols like insulin and influenza vaccines [18]. However, proteins can degrade during the process due to shear stress and air-water interface pressure. Adding stabilizing excipients, such as polysorbate 20, mitigates protein denaturation and enhances stability [19].

- Supercritical fluid technology

  Supercritical fluid [SCF] technology is a modern method for preparing particles with specific physicochemical properties for Dry Powder Inhalers [DPIs]. Using supercritical solvents like CO2 at high temperatures and pressures, SCF allows precise control over particle size, density, and polymorphism. This eco-friendly, single-step process produces micron- or nano-sized particles with narrow size distributions. SCF is used for inhaled APIs such as ipratropium and budesonide. CO2, a non-toxic alternative with a low critical temperature, is commonly used. SCF methods, including Solution Enhanced Dispersion by Supercritical Fluids [SEDS], create particles with superior flow and dispersion properties. Unlike jet milling, SCF avoids amorphous phase formation, maintaining aerosol performance even at high humidity [20].

***Types of DPIs***

DPIs are available in single-dose and multi-dose device designs, among others [21]. The different types of DPI inhalers is represented in the Figure 4. Certain DPIs release the drug only when the patient inhales; this type of DPI is called breath-actuated [22].

**Respiratory applications of DPIs**

An inhalation device called a dry powder inhaler [DPI] is used to inhale medication directly into the lungs in the form of a powder. They are frequently employed in the treatment of respiratory conditions such chronic obstructive pulmonary disease [COPD] and asthma [23]. Compared to conventional inhaler devices, DPIs provide a number of benefits, including as breath-actuated dosage, portability, and convenience of use. These are a few respiratory DPI applications [24].

**Asthma, chronic obstructive pulmonary Disease [COPD], maintenance therapy, rescue medication, combination therapy, patient preference, pediatric use**

***Significance of DPI in respiratory medicine (Table 1)***

- Efficient drug delivery: In the form of a dry powder, DPIs administer medication straight to the lungs. The powder's ideal particle size allows it to enter the respiratory system deeply and absorb effectively [25].
- Quick start of action DPIs are especially useful for treating acute symptoms linked to diseases like asthma and chronic obstructive pulmonary disease [COPD] because of their rapid onset of action [26].
- Convenience for patients and compliance: DPIs don't need complicated handling or synchronization, and they are frequently easy to operate. Because of their convenience and mobility, patients take their medications as directed, which improves patient compliance [27].
- Diminished Environmental Effects: DPIs don't pollute the environment like propellant-using pressurized inhalers do. DPIs are more environmentally friendly because they don't require propellants, which is consistent with sustainable healthcare practices [28].
- Drug Stability: For some drugs, especially those that are prone to deterioration in liquid form, dry powder formulations often offer improved stability. This constancy adds to the durability and effectiveness of the medications supplied by DPIs [25].
- Personalization of Recipes: DPIs make it possible to tailor medication compositions to each patient's unique need. This formulation flexibility can be very important for customizing therapy to meet the needs of each patient [26].

- Patient-Specific Factors: Age Different ages require different formulations or devices that would suited for their specific age group such as children, adults and the elderly [27].
  - Lung Capacity: The degree of inhaler resistance and the properties of the powder that is dispensed should be matched to the force with which the patient breathes in.
  - Disease Severity: Providing recommendations for dosage and describing how the dosage will be modified for varying respirations irresponsibility.
  - Comorbidities: Taking into account the other medical conditions which may predispose to alteration in the use of the inhaler or metabolism of the drug [28].
- Drug Formulation: Dosage Adjusting the amount of the active pharmaceutical ingredient present in the medicine to fit the required therapeutic profile of the patient.
  - Combination Therapy: Prescribing inhalers in which there is more than one API in order to cater for conditions that require the use of more than one substance.
  - Particle Size: Changing the properties of the particles and/or the flow of the aerosol stream in order to deposit material more effectively in the desired region of the lungs [29].
- Excipients:
  - Selection: Changing the carrier [for instance, from lactose to mannitol] or other downstream components to enhance the stability of the drug during storage, its solubility and/or digestibility by the body, as well as the patient's level of comfort while taking the formulated medicine.
  - Concentration: Modifying the API to excipients ratio to widen the surface area that will assist disperse the API and absorb it.
- Device Design:
  - Ease of Use: Creating equipment that is more user-friendly for particular patient populations, including young children or elderly people.
  - Dose Counters: Utilizing dose counters to enhance dosage administration
  - Inhaler Resistance: Modifying the resistance to correspond with the patient's rate of inspiration [30].

**Strategies for personalization**

- Reduction of Systemic Adverse Effects: DPIs reduce the amount of medication that is absorbed throughout the body by administering it directly to the respiratory system. The risk of systemic adverse effects, which are frequently connected to oral drugs, is decreased by this targeted distribution. Table 2 describes the benefits of DPI in personalized therapy.

- Handling Prolonged Illnesses: When it comes to treating long-term drug adherence—which is essential for both symptom control and disease management—DPIs are especially helpful in the management of chronic respiratory illnesses like asthma and COPD [31].

**Emerging trends in non-respiratory application**

***Introduction to systemic delivery via DPIs***

Dry powder inhalers [DPIs] primarily treat respiratory disorders like asthma and COPD, but recent advancements enable systemic drug delivery through pulmonary systemic distribution. This method deposits medication in the lungs, where it is absorbed into the bloodstream, leveraging the lungs' large surface area and vascularization for quick and efficient absorption. Benefits include targeted medication delivery to specific tissues or organs, improved bioavailability and pharmacokinetics, and avoidance of gastrointestinal and liver first-pass metabolism. Additionally, DPIs offer a non-invasive, user-friendly option, enhancing patient compliance. Pulmonary systemic distribution via DPIs presents a promising therapeutic approach for various systemic illnesses [32].

***Examples of drugs administered systemically using DPIs***

A number of medications have been studied for systemic administration using dry powder inhalers [DPIs]. Although the majority of DPIs are now administered locally to the lungs, researchers are looking into the possibility of using this route for systemic absorption to treat a variety of ailments [32]. Table 3 summarizes the various drugs and excipients employed in dry powder inhaler (DPI) formulations. The following are a few instances of medications that have been researched or created for systemic distribution by DPIs:

***Vaccination through inhalation [33].***

Inhalable vaccines aim to induce immune responses in the respiratory tract by targeting mucosal surfaces, eliciting both local and systemic immunity. These vaccines deliver antigens directly to the lungs, bronchi, and nasal passages, enabling efficient uptake by immune cells and triggering local immune responses. Inhalable vaccines stimulate mucosal immunity by promoting secretory IgA antibodies, which neutralize infections at mucosal surfaces. They also generate systemic immune responses, enhancing overall vaccine efficacy.

A key benefit is needle-free administration, offering a painless alternative to injections and eliminating the need for medical personnel and the risk of needle-stick injuries. Inhalable vaccines often use dry powder formulations, providing improved stability and reducing the need for cold chain storage. They can induce rapid immune responses, essential during respiratory disease outbreaks, and facilitate mass vaccination due to easy self-administration.

However, optimizing formulations, delivery methods, and ensuring long-term safety and immunogenicity across diverse populations remain challenges requiring further research.

## Treatment of localized conditions

### *Ocular conditions and DPIs*

Compared to more conventional approaches such as eye drops, ointments, or systemic drugs, the use of dry powder inhalers [DPIs] for treating ocular disorders is a relatively new and developing field of research. An summary of the benefits utilizing DPIs to treat eye disorders is provided here [34].

- Targeted Administration of Medicines: It is possible to create DPIs that are specifically intended to administer drugs to the posterior segment of the eye or the ocular surface. Using a targeted approach could decrease systemic adverse effects while increasing therapeutic efficacy and absorption [34].
- Longer Shelf Life and Better Stability: Dry powder medications have a higher stability than liquid ones. Less of the potentially ocular irritating preservatives needed [35].
- Patient Adherence: Easier to use than conventional eye drops or ointments, which can be irritating and call for accuracy. Possibility of less frequent dosing because of formulations with sustained release [36].

## Current research and applications

- Glaucoma: Investigating DPI delivery systems for intraocular pressure-lowering drugs. In contrast to daily eye drops, try to increase patient compliance [37].
- Ocular Inflammation and Infections: In order to treat infections or inflammatory disorders like uveitis or conjunctivitis, studies are looking into the use of DPIs to administer antibiotics or anti-inflammatory medications [38].
- Macular Degeneration: There is currently research being conducted on the delivery of medicinal drugs using DPIs directly to the posterior portion of the eye. This might offer an inconspicuous substitute for intraocular injections [38].

## DPIs in dermatological treatments

The application of dry powder inhalers [DPIs] in dermatological treatments is an evolving field of interest due to the distinctive advantages presented by dry powder formulations. This section provides a comprehensive examination of the potential benefits, associated challenges, and contemporary research concerning the use of DPIs in dermatology [39].

- Enhanced Stability and Longevity: Dry powder formulations generally exhibit greater stability compared to liquid or semi-solid alternatives, such as creams and gels. These formulations offer extended shelf life and reduce the necessity for preservatives, which can often cause skin irritation [39].
- Optimized Drug Delivery: Targeted delivery to specific skin areas can enhance treatment efficacy. Potential for sustained and controlled release, thereby reducing the frequency of applications required [40].
- Non-Greasy Application: Dry powders provide a non-greasy alternative to traditional creams and ointments, improving patient comfort and adherence to the treatment regimen. They allow for easier application and faster absorption without leaving a residue.
- Minimized Contamination Risk: Single-dose DPI devices can significantly reduce the risk of contamination compared to multi-use containers of creams or ointments.

**Challenges and considerations in the formulation of DPI**

Formulation and Particle Size Optimization: Developing effective dry powder formulations that adhere well to the skin and facilitate adequate drug absorption is complex. Ensuring optimal particle size is crucial to maintain powder adherence to the skin surface and prevent it from becoming airborne, which could reduce efficacy or pose inhalation risks.

- Effective Delivery Mechanisms: Designing devices that can uniformly and effectively deliver dry powder to the skin. Ensuring the delivery system is user-friendly and suitable for varying skin conditions and body areas.
- Bioavailability and Absorption: Ensuring the active pharmaceutical ingredient [API] is effectively absorbed through the skin barrier. Overcoming the stratum corneum, the outermost skin layer, which serves as a significant barrier to drug penetration.
- Safety and Irritation Potential: Assessing the potential for skin irritation or allergic reactions to the dry powder formulation. Long-term safety data are essential to confirm no adverse effects from prolonged use.

**Current research and applications**

- Psoriasis and Eczema Treatment: Research focuses on DPIs delivering corticosteroids and anti-inflammatory agents, offering a non-greasy, easy-to-apply option to enhance adherence.
- Acne Management: DPIs are being explored for delivering antibiotics and retinoids, reducing the oily residue of conventional treatments.

- Wound Healing and Infection Prevention: DPIs deliver antibiotics to promote healing and prevent infections, maintaining a dry wound environment.
- Cosmetic Applications: DPIs can deliver active ingredients for anti-aging, skin lightening, and moisturizers, offering a convenient application.
- Future Prospects: Advanced formulations, innovative delivery devices, and extensive clinical trials will drive the successful integration of DPIs into dermatology [41].

**Novel formulations for non-respiratory medications**

The advancement of novel formulations for dry powder inhalers [DPIs] targeting non-respiratory applications has expanded drug delivery possibilities. These innovative formulations enhance medication stability, bioavailability, and efficacy. Key advancements include:

***Lipid-based formulations***

Solid Lipid Nanoparticles [SLNs]: Improve bioavailability and stability by protecting sensitive drugs and controlling release rates.

Nanostructured Lipid Carriers [NLCs]: Offer higher drug loading and improved release profiles, particularly effective for lipophilic drugs.

Polymer-Based Formulations:

Biodegradable Polymers: Materials like PLGA and chitosan provide sustained drug release and can be tailored for specific kinetics.

Hydrogels: Engineered to release drugs in response to stimuli [e.g., pH, temperature], allowing controlled and targeted delivery.

***Protein and peptide formulations***

Stabilization Techniques: Methods like lyophilization and spray drying enhance shelf life and therapeutic effectiveness.

Encapsulation and Carrier Systems: Protect drugs from degradation and facilitate controlled release and enhanced absorption.

**Vaccine formulations**

Adjuvants: Boost immune response, making vaccines more effective.

Mucosal Delivery: Targets mucosal surfaces to induce systemic and mucosal immunity.

**Hormone and enzyme formulations**

Hormone Replacement Therapies: Deliver hormones like insulin or growth hormone, protecting them from degradation and enhancing absorption.

Enzyme Replacement Therapies: Improve stability and delivery efficiency for conditions like lysosomal storage disorders.

**Antimicrobial and antiviral formulations**

Direct Application: For localized infections, delivering high concentrations of agents directly to the affected area.

Controlled Release: Maintain therapeutic drug levels over extended periods, enhancing efficacy and reducing dosing frequency.

These advancements in DPI formulations represent significant progress in drug delivery technology. By leveraging various carriers, polymers, stabilization techniques, and targeted delivery systems, these innovations broaden the potential applications of DPIs beyond respiratory diseases, offering new treatment options for diverse medical conditions [42].

**Properties and evaluation of DPI (Table 4)**

***Properties of DPI:***

- Particle Size Distribution: Optimal Size Particles should be in the respirable range [1-5 micrometres] for effective lung deposition.
- Flow Properties: Flowability: Ensures consistent dosing and easy dispersion.
- Hygroscopicity: Ability to resist moisture absorption.
- Drug-Carrier Interaction: Adhesion Proper balance between API and carrier particles to ensure efficient drug delivery.
- Powder Dispersion: Aerosolization Efficiency The ability of the powder to disperse into fine particles upon inhalation.
- Stability: Chemical and Physical Stability Ensures the formulation remains effective over its shelf life.

**Challenges and future perspectives**

***Current limitations in non-respiratory DPI applications***

Despite considerable advancements in dry powder inhalers [DPIs] for non-respiratory uses, several challenges and limitations must be addressed to fully realize their potential. These challenges include issues related to formulation, delivery mechanisms, regulatory hurdles, and patient compliance [43].

**Formulation challenges**

- Particle Size and Uniformity: Achieving the optimal particle size for effective delivery and absorption is complex. Particles must be small enough to adhere to the target area but not so small that they become airborne and pose inhalation risks. Maintaining consistent particle size distribution is essential to ensure uniform dosing and therapeutic effectiveness.
- Stability of Active Ingredients: Many non-respiratory drugs, especially proteins, peptides, and vaccines, are sensitive to environmental conditions and may degrade during the formulation and storage process. Ensuring the stability of these active ingredients in dry powder form remains a significant challenge [44].

**Delivery mechanism constraints**

- Device Design: Creating DPI devices that effectively deliver non-respiratory medications to various target areas [e.g., skin, nasal mucosa] is challenging. The device must ensure precise dosing, adequate dispersion of the powder, and be user-friendly to enhance patient compliance.
- Site-Specific Delivery: Non-respiratory applications often require the drug to be delivered to specific sites, such as the skin or mucosal surfaces. Ensuring that the dry powder reaches and remains at the intended site without being lost during application is a critical challenge.

  Bioavailability and Absorption
- Overcoming Biological Barriers: The absorption of drugs delivered via DPIs can be impeded by biological barriers such as the stratum corneum in the skin or mucosal barriers in the nasal cavity. Developing formulations and delivery mechanisms that can effectively penetrate these barriers is essential.
- Variable Absorption Rates: The rate at which different patients absorb medications can vary widely, leading to inconsistent therapeutic outcomes. Addressing these inter-patient variations in absorption is necessary for reliable treatment efficacy [45].

**Safety and irritation**

- Irritation and Sensitivity: Dry powder formulations, particularly those containing adjuvants or stabilizers, can cause irritation or allergic reactions in some patients. Ensuring that formulations are well-tolerated and do not induce adverse effects is crucial for patient safety and compliance.

- Long-Term Safety Data: Comprehensive long-term safety studies are required to understand the chronic effects of non-respiratory DPIs. This data is essential for gaining regulatory approval and ensuring patient safety over prolonged use [46].

**Regulatory and manufacturing challenges**

- Regulatory Approval: Securing regulatory approval for novel DPI formulations and devices can be a lengthy and complex process. Regulatory agencies require extensive data on safety, efficacy, and quality control, which can be challenging to generate for new technologies.
- Scalability and Manufacturing: Scaling up the production of DPI formulations while maintaining quality and consistency poses significant manufacturing challenges. Ensuring that the manufacturing process is cost-effective and meets regulatory standards is essential for commercial viability.

  The current limitations in non-respiratory DPI applications underscore the need for continued research and innovation. Addressing these challenges requires a multidisciplinary approach involving advances in formulation science, device engineering, and regulatory strategies. Overcoming these obstacles will pave the way for broader adoption of DPIs in non-respiratory therapies, offering patients more effective and convenient treatment options [47].

**Addressing safety concerns and regulatory challenges**

Ensuring the safety of dry powder inhalers [DPIs] for non-respiratory applications necessitates thorough research, testing, and regulatory oversight. Key safety concerns include:

- Irritation and Allergic Reactions:

  Formulation Components: Adjuvants, stabilizers, and carriers in DPI formulations may cause skin irritation or allergic reactions. Extensive preclinical and clinical testing is vital to identify and mitigate these risks.

  Patient Monitoring: Continuous post-market surveillance and diligent patient monitoring are essential for timely detection and management of adverse reactions.

  Long-Term Use

  Chronic Exposure: Evaluating prolonged exposure to DPI formulations, especially for chronic conditions, is crucial to assess cumulative toxicity and long-term side effects.

  Biocompatibility: Ensuring biocompatibility of DPI components prevents adverse immune responses and mitigates risks associated with extended usage.
- Inhalation Risks:

Particle Size Control: Maintaining strict control over particle size is essential to prevent inadvertent inhalation, particularly for topical or mucosal delivery formulations.

- Contamination and Sterility:
  Manufacturing Standards: Adherence to stringent manufacturing standards is crucial to prevent contamination and ensure sterility, especially for biological agents.
- Packaging and Handling: Proper protocols are indispensable to maintain sterility and integrity throughout shelf life and minimize contamination risk.
  Navigating the complex regulatory landscape for non-respiratory DPIs presents challenges that must be addressed to obtain approval and ensure patient safety [48].
- Regulatory Approval Process:
  The regulatory approval process for dry powder inhalers [DPIs] for non-respiratory uses involves comprehensive documentation of safety, efficacy, and quality. Figure 5 illustrates the sequential steps involved in the regulatory approval process for dry powder inhalers (DPIs). Robust preclinical and clinical trial data are essential, along with standard harmonization across jurisdictions. Clinical trials must be meticulously designed, with meaningful endpoints aligned with treatment goals. Quality control and manufacturing processes must ensure consistency, reproducibility, and scalability to meet demand. Post-market surveillance is crucial for continuous monitoring of DPI safety and effectiveness, with systems in place to manage adverse events and maintain regulatory compliance. Addressing these challenges ensures patient safety and regulatory approval, making DPIs a promising option for personalized treatments in various medical fields [49].

**Future perspectives**

This review explores future trends of DPIs beyond respiratory ailments, recommending broader healthcare applications. DPIs offer effective solutions for dermatological treatments like psoriasis and eczema with improved drug stability and targeted delivery. They present new therapeutic platforms for ocular conditions such as glaucoma and dry eye syndrome, providing enhanced stability and controlled release. For vaccine delivery, DPIs offer stability and ease of administration, crucial for complex immunization programs in resource-poor countries. DPIs also provide a safer approach for hormone and enzyme therapies, ensuring precise dosing. They enable high concentrations of antimicrobial and antiviral agents for localized infections and quick pain relief for chronic conditions. Key benefits include enhanced stability, improved patient compliance due to non-invasive administration, and targeted delivery, increasing therapy effectiveness while reducing side effects. However, challenges such as formulation development, potential irritation, regulatory issues, and production scalability must be

addressed through further research and development. Responding to these challenges is essential for the future of DPI technology [23].

## Conclusions

Looking at dry powder inhalers for non-respiratory purposes has various exciting implications in drug delivery. Thus, with further research, practice, and cooperation, the DPIs currently face challenges and continue to offer improved, safer, and more convenient treatment. This will foster better health to patients and enhance health care delivery. The future looks bright for DPIs since they are biomedical devices that are capable of delivering multiple therapeutic services for as many disease types.

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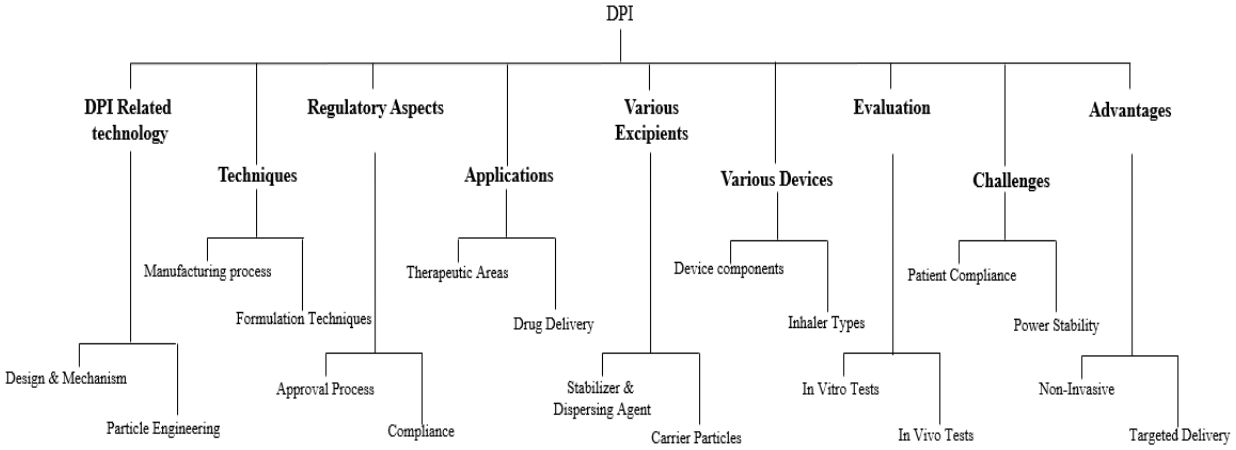


**Figure 1. Overview of DPI [3].**

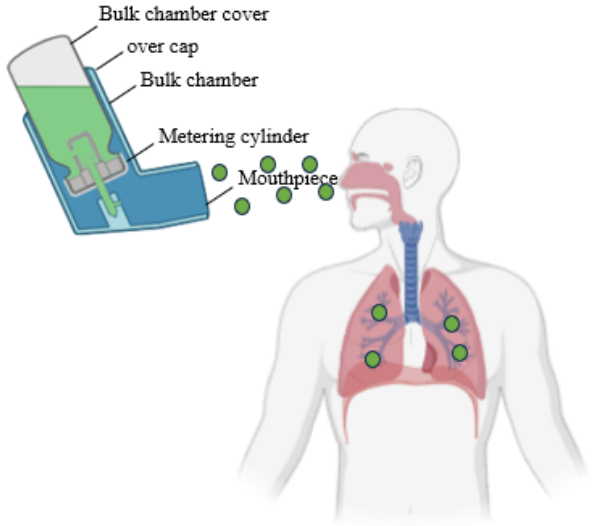


**Figure 2. Mechanism of DPI [6].**

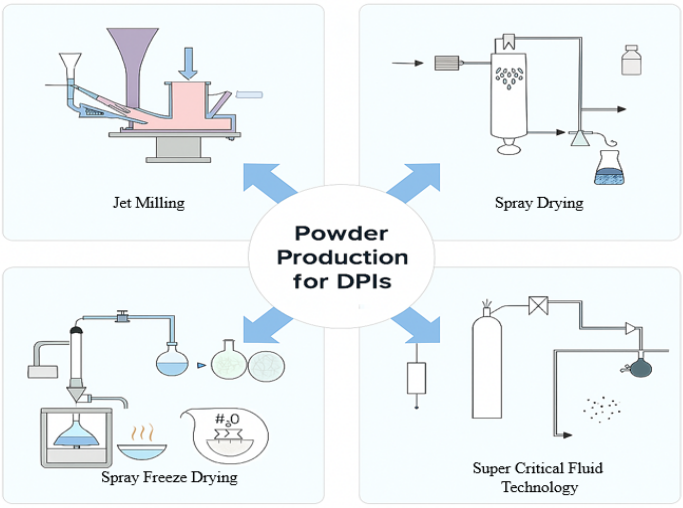


**Figure 3. Powder production for DPI [8].**

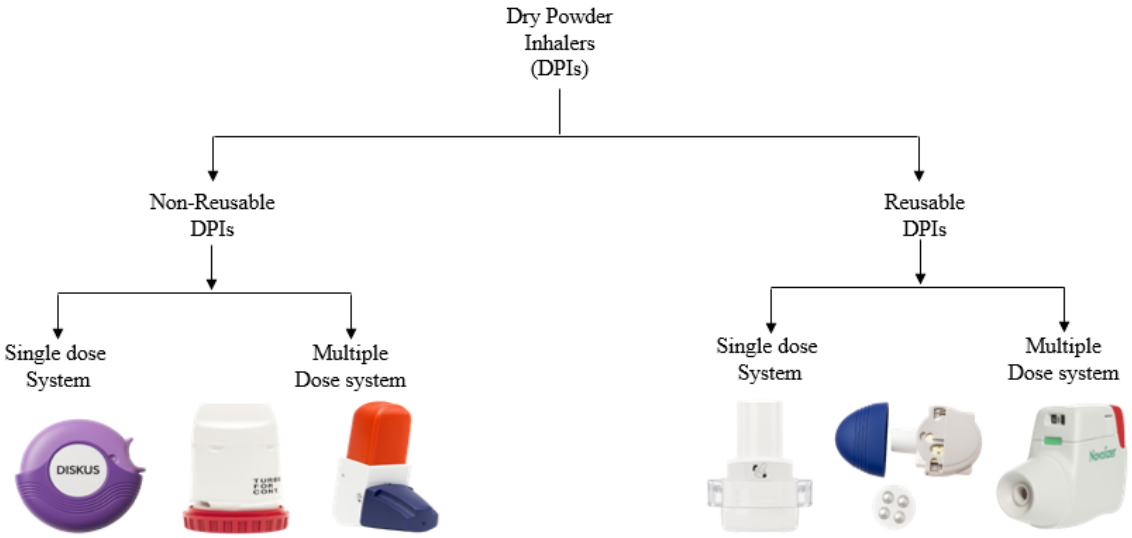


**Figure 4. Types of DPI inhalers [20].**

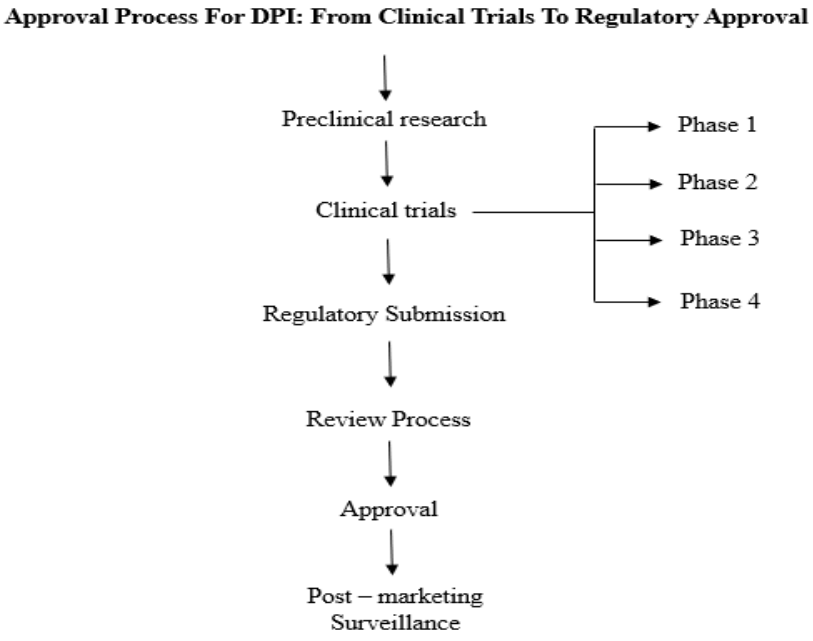


**Figure 5. steps involved in regulatory approval in DPI [49].**

**Table 1. Advantages of DPIs in asthma and COPD management [24].**

| # | Benefit | Description |
|---|---|---|
| 1 | Ease of use | Simple to use, suitable for individuals with poor manual dexterity, no need for canister pressing like in MDIs. |
| 2 | Portability | Small and easy to carry, promoting adherence to treatment regimens. |
| 3 | Breath-activated | Activated by inhalation, no hand-breath coordination needed, ideal for elderly and young patients. |
| 4 | Stability of medication | Dry powder formulations are more stable and resistant to temperature and humidity, ensuring long-term efficacy. |
| 5 | No propellant | Environmentally friendly, no aerosol releases, suitable for environmentally conscious patients. |
| 6 | Reduced risk of thrush | Direct lung delivery reduces the risk of oral thrush compared to some corticosteroid MDIs. |
| 7 | Variety of formulations | Suitable for various drugs like corticosteroids and bronchodilators, allowing customized treatment plans. |
| 8 | Potential cost savings | Initial cost higher but may save money in the long run as they don't require regular canister replacement. |
| 9 | Low maintenance | Requires less care compared to other devices like nebulizers. |

**Table 2. Personalized DPI formulation for different patients [26].**

| Benefit | Description |
|---|---|
| Portability | Patients can carry DPIs effortlessly because they are frequently small and lightweight. |
| Sustainability | DPIs are environmentally beneficial because they don't need propellants. |
| Stability | Certain drugs, particularly those that are moisture-sensitive, frequently have superior stability in DPIs. |
| Common application | DPIs are mostly used to treat respiratory diseases such as COPD, chronic bronchitis, and asthma. |
| Focused Relief | They provide immediate, focused comfort by delivering medicine directly to the airways. |

**Table 3. Different drugs and excipients used in DPI formulations [32].**

| # | Drug | Category | Function | Excipients | Remarks |
|---|---|---|---|---|---|
| 1 | Salbutamol | β-2 agonist | Bronchodilator for asthma and COPD | Lactose | Quick relief for asthma symptoms |
| 2 | Formoterol | Long-acting β-2 agonist | Long-term bronchodilator for asthma and COPD | Lactose | Provides long-lasting control of asthma symptoms |
| 3 | Budesonide | Corticosteroid | Anti-inflammatory for asthma and COPD | Lactose, Mannitol | Reduces inflammation in the airways |
| 4 | Tiotropium | Anticholinergic | Long-term bronchodilator for COPD | Lactose | Used for maintenance treatment of COPD |
| 5 | Fluticasone | Corticosteroid | Anti-inflammatory for asthma and COPD | Lactose | Helps control long-term asthma symptoms |
| 6 | Indacaterol | Long-acting β-2 agonist | Long-term bronchodilator for COPD | Lactose | Provides sustained bronchodilation |
| 7 | Mometasone | Corticosteroid | Anti-inflammatory for asthma | Lactose, Mannitol | Used for maintenance treatment of asthma |
| 8 | Umeclidinium | Anticholinergic | Long-term bronchodilator for COPD | Lactose | Used for maintenance treatment of COPD |
| 9 | Vilanterol | Long-acting β-2 agonist | Long-term bronchodilator for asthma and COPD | Lactose | Often combined with corticosteroids for synergy |
| 10 | Glycopyrronium | Anticholinergic | Long-term bronchodilator for COPD | Lactose | Improves lung function and reduces COPD symptoms |
| 11 | Beclomethasone | Corticosteroid | Anti-inflammatory for asthma | Lactose, Mannitol | Used for maintenance treatment of asthma |
| 12 | Aclidinium | Anticholinergic | Long-term bronchodilator for COPD | Lactose | Used for maintenance treatment of COPD |

**Table 4. Evaluation and properties of DPI [43].**

| # | Property | Evaluation Method | Significance |
|---|---|---|---|
| 1 | Particle Size Distribution | APSD using Impactors [e.g., NGI] | Ensures effective lung deposition |
| 2 | Flow Properties | Angle of Repose, Carr's Index, Hausner Ratio | Ensures consistent dosing and ease of use |
| 3 | Drug-Carrier Interaction | Adhesion and Cohesion Tests | Optimizes drug delivery efficiency |
| 4 | Powder Dispersion | Aerosolization Tests, FPF | Ensures proper dispersion into the lungs |
| 5 | Stability | Long-term and Accelerated Stability Studies | Ensures efficacy over shelf life |
| 6 | Drug Content Uniformity | Content Uniformity Tests | Ensures each dose contains correct API amount |
| 7 | Moisture Content | Karl Fischer Titration | Prevents clumping and maintains flowability |
| 8 | Device Performance | Delivered Dose Uniformity, Device Resistance | Ensures consistent and easy drug delivery |
| 9 | Patient Acceptability | Usability Studies, Inhalation Effort Tests | Ensures the device is user-friendly and effective for patients |