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Dry Powder Inhalers in Asthma Therapies: Recent Advances in Formulation Design and clinical Applications

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Abstract
Background:
The fact that dry powder inhalers (DPI) allow patients to administer their medications independently without the use of propellants has facilitated their global adoption as a means for administering asthma medication via inhalation technique. There has been an improvement in the effectiveness of drug deposition in the lungs as a result of advances made to aerosol delivery systems and powder technology. However, there remain some challenges with the use of the DPI device itself, including the device's design/composition, and the patient's ability to effectively use the DPI.
Method:
This is a summary of the issue involved with developing, making, and using a dry powder inhaler (DPI). Factors that impact the formulation and device and manufacturing issues are listed.
Results:
The major issue with a DPI is that the drug is dependent up on the inhaler being able to create enough force for delivery. The size distribution of the drug particles and the aerodynamic properties will also impact the amount of drug delivered to the lungs. Additional issues are the limitations of using a carrier (for example lactose), the variability from the process, the stability of the formulation, and the ability of the manufacturer to scale up production-especially for multi-drug formulations or nanotechnology -based drugs. The manufacturer must monitor and ensure each quality attribute throughout the manufacturing process to produce a successful DPI.
Conclusion:
The above issues highlight the need to develop better devices to deliver DPI formulations and better ways to formulate DPI to improve patient use

Key words: Particle engineering, lung deposition, asthma control, smart inhalers, and dry powder inhalers

I. Introduction:

ADPI is still reliant on the patient's breathing capacity despite these advancements. The powder won't enter the lungs deeply if the breath isn't strong enough. This requirement is very similar to that of nebulizers and A systematic review of the clinical effectiveness of dry powder inhalers in maintenance treatment and in treatment of acute exacerbations of asthma in children. The efficacy of DPIs is still impacted by a number of issues in practical application. The primary problem is that because everyone breathes differently, the inhaler's performance varies from person to person. Because every DPI has a different way of loading and inhaling the dose, some patients also find the devices confusing. The kinds of excipients that scientists can use are restricted when it comes to formulation, and each device's design affects how easily the particles separate and enter the lungs**.** The main issue is that different people have different breathing patterns, which causes the inhalers to perform differently. Due to the fact that each DPI loads and inhales the dose differently both medication delivery and patient adherence may be enhanced by these concepts. In the future, it will be crucial to match the formulation with the appropriate device and simplify the regulatory procedures. Improving the practical success of DPIs will also require clear and straightforward patient training.

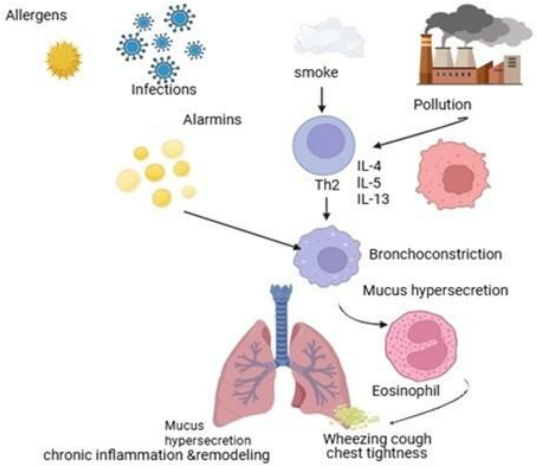

Figure 1: Pathogenesis of asthama

1 Inhaler types and limitations

Wheezing, dyspnea, and nocturnal cough are symptoms of asthma, a chronic inflammatory airway disease brought on by immune epithelial interactions **[1].** Eosinophilia, IgE production, and increased mucus secretion are the outcomes of abnormalities in the Th-2 high phenotype, which are caused by new immune mediators called alarmins like TSLP, IL-25, and IL-33. Individuals with a Th-2 low phenotype either don't react to corticosteroids at all or need higher dosages. The microbiome, environmental exposures, and genetics all have an impact on asthma, which makes it difficult to standardize treatment approaches **[1] [2].** Asthma is common in developed nations, with an estimated 300 million patients worldwide. Although managing asthma objectively lowers symptoms and future attack risks, mortality rates are still significantly higher in low -and middle -income countries, creating an unfair situation. The cornerstone of treatment is still inhaled medication therapy with metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers. Although MDIs are affordable and portable, they can cause inhalation coordination issues in severe asthmatics due to the inherent risk of human error, nebulized drug therapy permits high drug doses but is not practical for home use, and DPI overcome inhalation coordination issues and have no topical environmental impact, but medications can be susceptible to inspiratory flow and humidity **[3].** DPI have recently gained popularity due to their ease of use and sustainability. Dose variability and lung deposition have been enhanced by the development of engineered particles, densely packed carrier particles, and improved powder flow characteristics of drug formulations in DPIs **[4].** DPIs have the potential to deliver systemic and customized drug formulations in addition to being a helpful modality for managing and treating asthma symptoms. However, the most recent efficiency thresholds for drug delivery are frequently underestimated, and the actual performance of DPIs is frequently underestimated, and the actual performance of DPIs is frequently hindered by variations in inspiratory flow rates, dose, and pharmacokinetic and pharmacodynamic limitations of DPIs.

Table 1. A comparative analysis of traditional breathing devices for the treatment of asthma

Device Type	Era / Context	Delivery Mechanism	Key Pros	Key Cons	Clinical Notes	Examples / Innovations	References
Nebulizers	Early devices; acute care use	Aerosolize liquid via compressor/ultrasound /mesh	High dose, minimal coordination	Bulky, long use time, and cleaning are needed	10–15% lung deposition; best for severe/low-dexterity patients	Portable mesh, battery-powered	[3]
pMDIs	Mid-20th C; portable alternative	Pressurized canister, manual actuation	Compact, low-cost, drug-flexible	Coordination needed, frequent errors, no dose counter	8–16% lung deposition; spacers improve outcomes	Dose counters, extra-fine particle pMDIs	[3] [5]
DPIs	Late 20th C;	Micronized drug + carrier; inhaled powder	No coordination needed,	Inspiratory flow ≥35–60	10–32% deposition; lower	Turbuhaler, Diskus,	[3] [5], [6] [7]

	breath-actuated		higher deposition potential, and eco-friendly	L/min needed, humidity sensitive	doses possible	Novolizer with feedback cues	
SMIs	21st C; new tech	Spring-driven slow aerosol cloud	High deposition (40–50%), low oropharyngeal loss	Fewer drug options, higher cost	Good for low-flow patients	Respimat® reusable actuator	[3]

Abbreviations: C stands for century; L/min for litres per minute; DPI for dry powder inhalers, SMI for soft mist inhalers, and pressurized metered-dose inhalers.

1.1 Historical Development of DPIs

Smoke and fumes from herbal remedies ,such as Ephedra sinica and Datura ,Have been inhaled for respiratory benefits since ancient times [8]**.**However, the use of DPIs ,or dry powder inhalers ,in modern medicine actually started in the middle of the 20th century ,taking the place of larger devices or pressurized metered -dose inhalers (pMDIs), which needed a lot of coordination .The Abbot Aerohalor (1948),which added lactose -drug mixtures for better pulmonary delivery ,was the first commercial DPI . An important step toward more DPIs was the Spinhaler® (1967), which offered a breathing -actuated, pre-metered dose from capsules.[9] [10] [11]. With multi-dose and blister strip inhalers for dose protection and consumer usability, significant advancements in DPI were made during the 1970s and 1990s [12]. The 1987 Montreal protocol, which phased out ozone-depleting CFC propellants, played a significant role in this evolution. This accelerated the transition to propellent -free DPIs and new engineering techniques, such as carrier -free DPIs like the Turbuhaler®, which were used to guarantee high fine -particle fractions devoid of lactose. [13]. In order to maximize aerosolization and fine particle deposition, formation-device co-optimization using particle engineering techniques such as micronization, spray drying, and surface modification has become the trend in DPI development in the twenty -first century [10]. Current DPIs now include ergonomic mouthpieces, dose counters, low-resistance airways, and digitized feedback systems, demonstrating a fit-for-purpose and environmentally conscious design [10]. A useful summary of historical turning points is given in Table 2, which further illustrates how DPI evolution has been determined by both technological advancement and regulatory concerns. Notably, this trajectory illustrates the interdependence of clinical, industrial, and policy influences in the parallel evolution of inhaled delivery to inhaled medications and indicates that some advancements, though not always linear, were externally-triggered (i.e., environmental regulation).

Table 2. Important turning points in the history of dry powder inhalers (DPIs)

Era / Year	Device / Milestone	Key Technical Innovation	Clinical or Regulatory Impact	References
~1000 BCE–1500 BCE	Ancient inhalation practices (China, Egypt, Greece, and Rome)	Vapour from medicinal herbs (e.g., *Ephedra sinica*, *Datura*)	Early empirical recognition of inhaled therapy for respiratory relief	[8]
1852	Ira Warren coaxial glass tube inhaler	Early dry powder delivery via manual insufflation	Poor dispersion, inconsistent dosing	[8]
1889	Carbolic Smoke Ball	Rubber squeeze-ball powder delivery	Public interest in portable inhalation devices	[8]
1948	Abbott Aerohalor	First industrially manufactured DPI (lactose–drug blends)	Pulmonary delivery of penicillin, norethisterone	[8] [9]
1967	Filsons Spinhaler®	High-dose sodium cromoglycate in pierced gelatin capsules	Standardized carrier-based DPI design	[9] [10] [11]

1969–1990s	Rota haler®, Inhalator Ingelheim, Cyclohaler®	Variations in capsule-opening and dispersion	Improved patient usability	[9] [10]
Late 1980s	Turbuhaler®	Carrier-free spheronized soft aggregates	Higher fine-particle fraction, no lactose carrier	[9] [10]
1987	Montreal Protocol	—	CFC phase-out drove DPI innovation	[11] [12], [13]
1990s	Diskhaler®, Diskus®	Multi-unit dose blister packs	Dose protection, reduced handling steps	[10] [12]
1990s–2000s	Easyhaler®, Novolizer®	Multi-dose reservoir with integrated metering	High-dose capacity, ergonomic design	[10] [13]
2000s–present	Twisthaler®, PulmoSpheres™, digital DPIs	Engineered particles, feedback cues, digital monitoring	Consistent dosing, adherence support	[10][11][12] [13]

1. **Problems in asthma inhalation therapy: patient compliance, device, usability, dose consistency**

Due to obstacles involving patients, devices, healthcare systems, and socio-environmental factors, real-world asthma control is still subpar despite substantial device innovation [14] [15] [16]. Patient -related errors continue to be the primary cause of subpar results 28-46 % of DPI users make major errors, and up to 92 % make critical ones. These errors are typically caused by inadequate inspiratory effort, incorrect priming, incomplete exhalation, or inadequate breath - hold. young people, the elderly, and those with cognitive or motor impairments are more affected by these problems. The area of non-adherence is only made worse by behavioural problems, such as underestimating the severity of the illness, relying on a SABA, and /or fearing or comprehending ICS.[17] [18] [19]. The problem is further complicated by device-related problems. Dose delivery may ultimately be jeopardized when a patient's inspiratory capacity is incompatible with the device's airflow resistance, when DPI platforms differ, and when the device is susceptible to environmental factors like temperature and humidity [5] [20]. The health care gap is equally significant because prescribers frequently lack the training required to provide comprehensive inhaler education, do not regularly reevaluate inhaler technique, have few options for spirometry or biologics, or provide current, guideline-based care [19] [21]. Exacerbation and reduced adherence to treatment regimens are also influenced by socio-environmental factors, air pollution, the overall allergen burden, weather and climate variations, and socioeconomic disparities. While some of the obstacles to technique and general adherence with asthma management have been somewhat addressed by digital health solutions (such as apps, video modules, and QR-based training) and remote monitoring,**[14],** They are not used consistently. All things considered, managing asthma with a DPI requires more than just device advancements. Consistent and equitable results will result from a comprehensive approach to a patient-centered design that integrates the device innovations with professional education, personalized education, accessible diagnostics, and socioeconomic intervention.

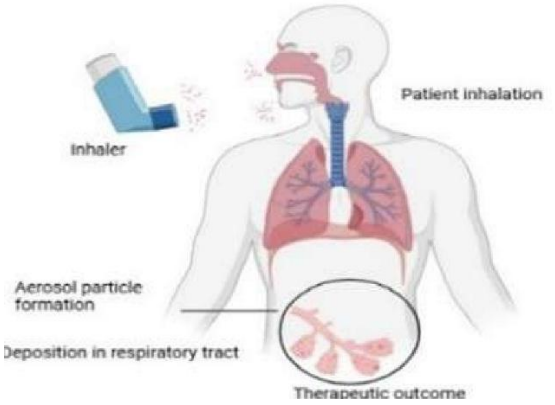

Figure.2: Schematic representation of inhalation drug delivery showing aerosol generation, respiratory tract deposition, and therapeutic outcome

3. Advances in DPI Formulation Technologies

In order to optimize aerodynamic performance, stability, and clinical efficacy in asthmatic patients, recent advances in DPI development have focused on modifying particle and carrier characteristics such as size, shape, density, and surface chemistry.[14]

3.1 Engineering for optimized Aerodynamic properties

Determining deposition requires knowledge of the aerodynamic diameter. Particles <0.5 µm are exhaled, particles >5 µm deposit oropharyngeally, and particles 1-3 µm are in the deep lung's conducting airways.[15] [16]. Furthermore, particle density and form are important dispersibility modifiers. Long,

porous, corrugated particles, for instance, can improve the proportion of tiny particles (FPF) by reducing cohesion.[17]. Controlling the form is becoming more and more possible; techniques like spray drying, freeze drying, PRINT®, and supercritical fluid processing enable more control over porosity and size.[17]. Force-controlling substances like leucine, magnesium stearate, and DPPC can lessen adhesion and electrostatics, while stabilizers like mannitol or trehalose can help prevent recrystallization. [18]. These developments all encourage aerosolization and may help control asthma.

3.2 Use of Excipients and carriers

Drugs that are micronized may have poor flow, necessitating the use of carriers. Although lactose is the typical regulatory carrier for inhaled drugs, other carriers like mannitol and trehalose offer stability from moisture and improve patient tolerability. [15]. Drug detachment is also influenced by the barrier surfaces' porosity and roughness. [14]. Co-crystals, aerogels, and hydroxyapatite are examples of more recent systems that may maximize a drug's aerosolization. [17]. Leucine, DPPC, and magnesium stearate are examples of additives that can increase FPF and decrease interparticle cohesion [18]. New excipients (such as chitosan, PLGA, cyclodextrins, and FDKP) enhance mucus penetration and deliver the medication to the lung in a targeted and prolonged manner [19]. Consequently, the choice of an excipient is now a strategic factor for enhancing dosage accuracy and safety, even though excipients were previously thought to be merely functional [20].

3.3 Novel Formulation strategies

In the end, sophisticated particle-engineering techniques aim to address the cohesion issue for micronized medications. Although coarse α-lactose monohydrate is still commonly used in carrier-based systems, porous lactose and engineered polyols (trehalose, erythritol, sorbitol) improve stability and fine particle fraction (FPF) [15] [16]. Systems based on mannitol or polyol have also been developed as a result of lactose intolerance. Aerosolization properties have been further enhanced by next-generation carriers such as lactose–mannitol co-crystals, porous aerogels, and calcium phosphate (hydroxyapatite)-structured porous particles. Leucine, phospholipids, and magnesium stearate are examples of force-control agents that work to restrict the powder's ability to absorb moisture. Fines-containing ternary blends can help separate powder, but they must be carefully balanced with the remaining powder blend or make up a small portion of the total weight to prevent the powder blend from becoming unstable. [18]. Additionally, new excipients that can aid in achieving solubility enhancement, mucosal targeting, or sustained release include chitosan, PLGA, hyaluronic acid (HA), cyclodextrins, and FDKP [15] [19]. The goal of the emphasized excipient innovations is to show that the right excipient chemistry and particle design are essential for DPIs to work consistently as a treatment.

3.4 stability and storage Considerations

Strict stability control parameters are necessary for a DPI to function effectively in preserving aerodynamic characteristics and dose uniformity. Moisture that causes agglomeration, cohesiveness, and FPF loss is the biggest stability risk, particularly in amorphous spray-dried powders [15] [16]. Leucine, trileucine, and magnesium stearate are hydrophobically prepared excipients that create surface barriers to prevent moisture sorption [17]. Recrystallization, polymorph transitions, and/or hydrates found in high-Tg excipients (such as pullulan and trehalose) and storage conditions significantly below the Tg are risks associated with amorphous APIs [17]. Frequently, photolysis, oxidation, and/or Maillard interactions—difficulties with reducing sugars—cause API degradation.[15]. Stability is directly related to the methods used to engineer the particles: freeze-drying creates systems that are porous but hydroscopic in stability, spray drying and powders offer good dispersion but are moisture sensitive, and supercritical fluids produce stable crystalline particles [18]. Product developers can detect the beginning of instability using analytical tools like PXRD, DSC, DVS, and AFM, and packaging techniques (desiccant capsules, Al–Al blisters) that adhere to ICH Q1A(R2) considerations can further safeguard product stability [19]. The development of DPI formulations demonstrates that particle engineering, excipient development, and stability control interact to drive clinical product performance rather than the inhaler's design alone. The main excipient is still lactose, but evolving particle design and development methods will inevitably promote the creation of biocompatible excipients (lactose substitutes) to update the distribution of inhalable formulations. In the future, formulations will also include moisture stability packaging, digital device feedback, and engineered excipients to preserve dose uncertainty and customized asthma management strategies.

4 Comparison between Pharmacokinetic and pharmacodynamic relevant to DPI Formulations

Pharmacokinetics (Pk)Relevant to DPI Formulations	**Pharmacodynamic (PD) Relevant to DPI Formulations**
Describes drug deposition, absorption, distribution, metabolism, and clearance after inhalation. [11]	Describes the magnitude, onset, duration of drug effect at pulmonary and systemic receptors. [11]
Aerodynamic particle size governs lung deposition,1 µm exhaled,>5 µm oropharyngeal, <5 µm reaches lower airways. [12]	Deposition site determines extent of receptor activation in central versus peripheral airways. [12]
Extra -fine particles (<2 µm) improve peripheral airway deposition. [12]	Enhanced distal airway receptor engagement improves asthma control. [12]
Systemic exposure is reduced by low oral bioavailability. (1%), strong plasma protein binding (≥98%), and quick clearance (<90 L/h) minimize systemic exposure. [12]	Reduced systemic exposure lowers adverse effects and improves safety.[12]
Lipophilicity and biphasic absorption influence pulmonary retention and systemic absorption of LABAs. [13]	Determines rapid onset followed by sustained bronchodilation.[13]
Device airflow resistance and required inspiratory flow (≥35–60 L/min) affect emitted dose and lung delivery. [14]	Inadequate inspiratory flow reduces bronchodilation and therapeutic response. [14]
Reservoir-based DPIs may increase systemic drug exposure. [15]	Increased exposure may worsen pharmacodynamic effects such as HPA -axis suppression. [15]
Patient factors such as age and airways obstruction influence inspiratory capacity and lung deposition. [13]	Reduced deposition leads to weaker pharmacodynamic response. [13]
Stereochemistry affects systemic absorption and distribution (R-enantiomer selectivity). [11]	Improved receptor selectivity with fewer systemic side effects (levalbuterol). [11]
Controls drug concentration at the site of action over time.[11]	Translates concentration into the therapeutic efficacy and safety. [11]

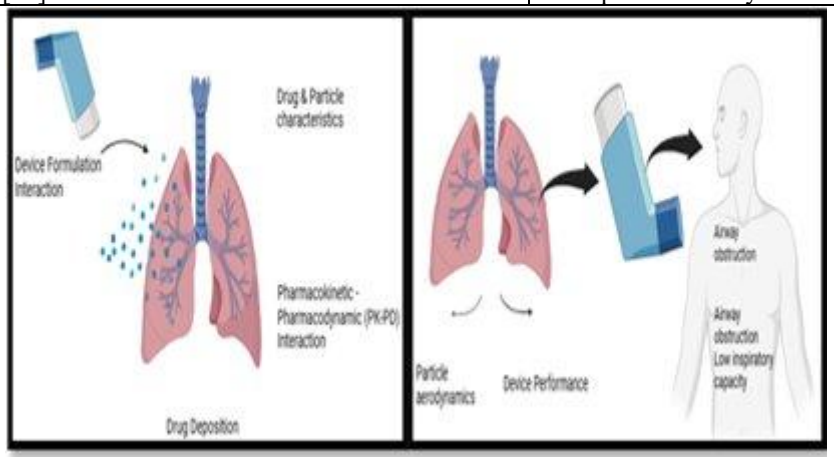

Figure 3: Comparison between Pharmacokinetic and pharmacodynamic relevant to DPI Formulations

Table 3. Pharmacokinetic (PK) determinants, pharmacodynamic (PD) outcomes, and clinical implications in DPI-delivered asthma therapy [1–6].

PK Determinant	PD Outcome	Clinical Implication	Ref.
Aerodynamic particle size (1–5 µm; extra-fine <2 µm)	Determines airway penetration depth; extra-fine enhances peripheral deposition	Improves anti-inflammatory efficacy; reduces oropharyngeal deposition	[3], [6]

Receptor-binding affinity (e.g., mometasone furoate, fluticasone propionate)	Prolonged receptor occupancy	Sustained anti-inflammatory action; allows reduced dosing frequency	[3]
Lipid conjugation (budesonide, ciclesonide)	Slow-release pulmonary depot	Extended duration; supports once-daily dosing	[3]
Low oral bioavailability (<1%)	Limits systemic exposure from swallowed fraction	Reduces systemic corticosteroid adverse effects	[3]
Prodrug activation in the lung (e.g., ciclesonide)	Minimizes oropharyngeal active drug	Lowers local side effects such as candidiasis	[3]
High plasma protein binding (≥98%)	Limits free circulating drug	Further reduces systemic toxicity	[3]
Rapid clearance (<90 L/h)	Short systemic half-life	Minimizes prolonged systemic effects	[3]
Inspiratory flow & device resistance	Influences deaggregation and lung delivery	Device–patient matching is critical for efficacy	[7] [9]
Device design (Turbuhaler® vs Diskus®)	Alters deposition patterns and systemic exposure	May require device-specific PK/PD evaluation	[7] [8] [9]
Airway obstruction	Reduces lung deposition and systemic absorption	Dose/device adjustment needed in severe asthma	[7] [9]
Enantiomer specificity (e.g., levalbuterol)	Improved bronchodilation at lower doses	Lower systemic side effect burden	[7] [9]

5. Clinical Applications and Efficacy in Asthma Management

Dry powder inhalers (DPIs), which were first designed to replace pressurized metered-dose inhalers (pMDIs), are now an essential part of asthma treatment for acute relief, maintenance, and newly developed digital support for adherence. The literature consistently demonstrates that DPIs are at least as effective, if not more so, than pMDIs and nebulizers when used by skilled users. However, in practice, the device's features have much less of an impact than the user's technique, training level, and overall inspiratory capacity (Table 4).

5.1 Recent Clinical Trials and studies on DPI Devices

The efficacy of dry powder inhalers (DPIs) in both pediatric and adult patients is supported by recent clinical trials, systematic reviews, and real-world audits. In 2025, a systematic review of 27 randomized controlled trials (RCTs) revealed that DPIs are comparable to pressurized metered dose inhalers (pMDIs) (with spacers) in children four years of age and older when peak inspiratory flow (PIF) thresholds were met [20]. Acute exacerbation studies demonstrate that dry powder inhaled SABAs, or short-acting beta-adrenergic agonists, are equal in efficacy to pMDIs and nebulizers. Between 4 and 94% of users have reported misusing their devices; the Turbuhaler has the lowest user error rate, while the Diskhaler has the highest [21] [22]. FEV_1, PEFR, and symptom control all significantly increase with structured and repeated training; however, in certain studies, up to 25% of patients are still unable to demonstrate the proper technique [23]. Real-time feedback and adherence monitoring are provided by smart inhalers like the Reliever Digihaler, which improves ACT scores and lowers SABA use [24]. Overall, device design, training intensity, and digital components—rather than just drug formulation and delivery pressures—are taken into account where outcomes occurred in clinical management of asthma, as highlighted across these studies (summarized in Table 4)

5.2 Comparative Effectiveness versus MDI vs Nebulizer

When comparing DPIs, pMDIs (with spacers), and nebulizers, head-to-head randomized controlled trials (RCTs) and observational studies consistently find no significant differences (oral, inhaled, or monitored) in lung function outcomes (FEV_1, PEF), symptom scores, or exacerbation rates.[20] [21]. However, when real-world usage rates of these devices are taken into account, this may change. Logistic regression indicates that pMDIs are misused more than three times more frequently than DPIs, with 50% of patients abusing DPIs and 76% abusing A systematic review of the clinical effectiveness of dry powder inhalers in maintenance treatment and in treatment of acute exacerbations of asthma in children [22] [23]. As mentioned, ergonomic devices (like a Turbuhaler or Diskus) might be less problematic, and digitally connected devices (like Connect1) might increase societal adherence because they track usage [24]. Despite being significant, formula differences are also among the least talked about. Extrafine particulate pMDIs, for instance, may outperform DPIs with smaller cohort clinical populations, indicating that formula properties may

outweigh device impact [25]. The trial differences used to present the aforementioned conclusions are shown in Table 4.

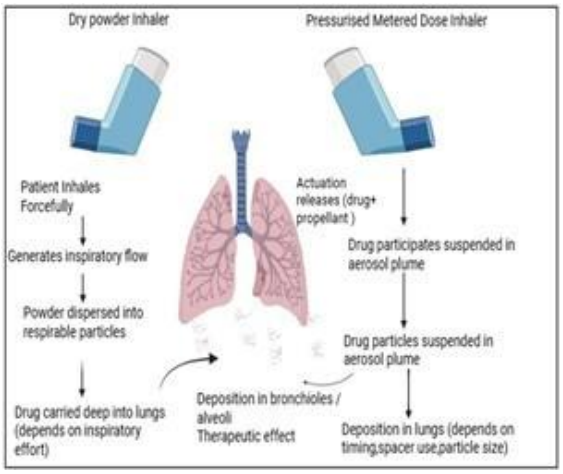

Figure 4: comparative effectiveness versus MDIs and Nebulisers

5.3 Safety and Patient Adherence Data

DPI safety profiles are similar to those of nebulizers and pMDIs. All of the inhalation categories have comparable systemic reactions and local side effects coughing, dysphonia, throat irritation [20]. The incapacity to effectively use capsule-based DPIs for children under six years old and the moisture sensitivity of bulk reservoir systems (such as Turbuhaler) are examples of device-specific limitations.[21]. The ease of use of the device and patient education have a direct impact on adherence to the regimen. In less than three days, over 33% of patients lose the proper technique, and 25% of patients say they have never received formal instruction.[21]. Dose counters and digital sensors (such as Propeller, Hailie®, and Digihaler) are examples of innovations developed to improve adherence and inhalation quality.[22]. Although there is still a knowledge gap regarding the use of corticosteroids, over 70% of people are satisfied with a DPI overall [23]. These observations about adherence and safety evidence are highlighted in Table 4. The aforementioned safety issues and low adherence highlight how crucial it is to design the device and teach the patient how to use it in order to optimize the therapeutic benefit.

5.3 Real -world Evidence and Patient – Reported outcomes

The effectiveness of dry powder inhalers (DPIs) is strongly supported by randomized controlled trials; however, real-world research and patient-reported outcomes (PROS) have revealed notable variations in DPI usability, acceptability, and long-term asthma management. Children as young as 4-5 years old can often generate sufficient inspiratory flow, and DPI is generally accepted by patients and caregivers if properly trained.[39]. A device's design has an impact on its efficacy. For example, only 11% of patients abuse an ergonomically designed device like the Aerolizer, compared to 68% who abuse a Diskhaler. Correct inhaler technique and/or adherence to inhalation medications have been linked to reduced symptoms at night, better control during the day, and a decreased need for rescue bronchodilators. Other crucial elements that enhance asthma patient outcomes include dose counters, portability, ease of handling, and a decreased need for spacers [20], [21] [22]. Extrafine pMDIs formulations were found to provide better asthma control than DPI ICS/LABA combinations in certain real-world evidence studies. These significant variations show how flow-dependent inhalation, aerosol plume, and particle size all affect results. Similarly, depending on their inhalation capacity, DPIs alone can improve patients' well-being and quality of life. They can also be very easy to use. These findings are a reflection of continuous training and feedback, and in order to attain the best results, it is critical that each patient receive the appropriate device.

Table 4. concise overview of clinical trials and literature related to dry powder inhalers for asthma treatment

Population	Intervention / Device	Comparator	Key Clinical Insights	References
Children ≤12 yrs (maintenance), ≤18 yrs (acute)	ICS or ICS/LABA via various DPIs	pMDIs+ spacer, nebuliser, placebo	High-certainty evidence: DPIs ≈ pMDIs in maintenance; viable in acute exacerbations with adequate technique; gaps in community-managed acute care data.	[20]
Mixed-age asthma patients	Various DPIs	pMDIs	Incorrect DPI use 4–94%; errors linked to reduced FEV_1 and control; training improves technique, but ~25% still fail after instruction.	[21]

Asthma & COPD patients	Sano haler, Handihaler, Diskus, others	pMDIs	DPI misuse 64% vs MDI 77.6%; lowest misuse in Sano haler (40%); errors: not exhaling before inhalation is the most common.	[22]
Adults 15–45 yrs, mild–moderate asthma	Budesonide via Rota haler, Diskhaler, Trans haler	Inter-device comparison	All DPIs improved FEV_1% & PEFR equally; reduced rescue use; training key to maintaining technique.	[23]
≥13 yrs, uncontrolled asthma	Reliever Digihaler (smart DPI)	Standard albuterol inhaler	Higher probability of ACT improvement; fewer SABA uses; enabled real-time inhalation monitoring.	[24]
Asthma, mixed age	Multiple DPI types	N/A	Deposition efficacy tied to inspiratory flow; older/severe patients at risk for suboptimal delivery; technique errors ~43%.	[25]
Asthmatic smokers	ICS/LABA/LAMA vs ICS/LABA via DPI	Dual therapy	Triple therapy improved small airway metrics & ACQ scores; supports tailored pharmacologic strategies.	[26]
Mild asthma	As required Formoterol/budesonide Turbuhaler	Budesonide + maintenance SABA	Reduced severe exacerbations by ~37%; maintained symptom control; supports simplified regimens.	[26]
Children 5–11 yrs	Low/medium-resistance DPIs	MDIs + spacer, nebuliser	90–97% achieve PIF threshold; technique poor at baseline but improves with education; acute phase PIF may drop.	[27]
Adults with persistent asthma	ICS/LABA via DPI	Extrafine BDP/F via pMDIs	Higher control rates & lower ICS doses with pMDIs suggest formulation & particle size can outweigh device type.	[28]
Mild–moderate asthma	Turbuhaler®, Novolizer®	Larger particle devices	1.5–3 µm particles achieve deeper lung deposition; higher inspiratory flow boosts bronchodilation.	[29]

6. Challenges Associated with dry powder inhalers in asthma management

Continuous improvements in aerosol delivery and drug formulation science technologies are finding it increasingly increasingly difficult to create effective, user-friendly DPIs due to the many factors preventing approval from the regulatory agencies. Patient's use, interaction with the device, the device design limitations, and the overall complexity of the formulation are all very influential in determining the performance and usability of DPIs. Particle size has been identified as a factor impacting lung deposition , studies have demonstrated that approximately those particles that exceed Particles smaller than 1 µm are mostly exhaled, and particles larger than 5 µm are deposited within the oropharyngeal passage[26], [27],.sound's aerodynamic diameter between 1 and 5µm allows for deeper lung deposition than other particle sizes .unfortunately successfully maintaining this size throughout drug product formulation ,aerosolization and delivery remains one of the largest challenges in developing an inhaler.

6.1 **Limitations**

The process of obtaining and maintaining an ideal particle size range is made even more difficult by issues related to particle agglomeration, the retention of the active drug on carrier particles, and the loss of fine drug particles for delivery via inhalation. These issues also limit the ability to effectively deliver either a fine particle via inhalation. Most commercial DPIs consist of micronized drug mixed or bound to large particles, and the flow rate

of the patient during inhalation also has a large effect on the amount of the dose emitted as well as the efficiency of deposition of the active drug. Inhalation technique, inhalation effort, the amount of the dose, and the delivery to the lungs of the active drug vary greatly based on the flowrate of the inhalation. Thus, individuals with asthma, children, the elderly, and those with extremely limited airflow capacity may not be generate sufficient inspiratory force to create optimal conditions for the performance of the DPI device. In addition, accidental exhalation of moisture will negatively affect the ability of the device to distribute powder and consistently deliver a uniform dose. For optimal dispersion and aerosolization of DPIs, patients must take a strong deep breath on a regular basis, however, any inability to do so will cause a significant reduction in the efficacy of the drug, Moreover the volume of powder delivered with each inhalation is limited by the physical construction of the DPI reservoir walls and the method for extracting powder from the reservoir. Although using carrier-based formulae will result in a more uniform flow of powder ,there will still be a significant problem ,because the strong adhesion between the drug and the carrier particles limits the maximum inhalation dose /or negatively affects the drug's efficiency for delivering to the lung , Even though there have been much progress in the engineering of particles for dispersion many of the same limitations remain in the drug formulation process,[26]. Common inhalation and handling errors can further decrease lung deposition through inhaler misuse, such as positioning of the inhaler incorrectly or failing to hold the breath long enough after using the inhaler and not completely the inhalation step correctly. Patient-related errors are very common therefore; patients need to receive ongoing education to enhance their ability to attain favorable clinical results [26]

6.2 **Future Directions in dry powder Inhaler Development**

DPI will become more individualized in the future to maximize medication delivery and boost clinical effectiveness, looking at each patient individually ,including their inhalation capacity ,the degree of their disease, and how well their lungs function .Digital dispensing devices ,for example ,are being developed through the use of smart sensors and mobile applications ,and it will be possible to monitor how a patient uses their inhaler in real-time and enhance their compliance to the assigned dose via the data collected in this manner[26. While this is ongoing, research is also investigating the potential for many types of inhaled medications and biopharmaceuticals being delivered via DPIs for treating not only people with asthma but also for other respiratory illness and systematic diseases [26]. In addition, reductions in environmental impact while providing functional design and user- friendliness by using sustainable production methods and eco-friendly materials is becoming a growing focus of current and future DPI designs.

6.3 Current Limitations in Formulations and Device Technologies

The most pressing problem is the formulation of lactose, the main carrier, which promotes Maillard reactions with amine medications and results in intolerances in patients who are sensitive, and aerosolization is less ideal due to the high humidity [30] [31**.** The amount of incorporation of biodegradable polymers (PLA, PLGA) or nanoparticle carriers is limited due to safety, stability, and regulatory concerns. Other excipients, such as phospholipids (DPPC) and magnesium stearate, improve stability and decrease cohesion **[**32] [33**]** Technically speaking, it can be challenging to operationalize athletic or aerodynamic diameters smaller than 5 μm, which frequently leads to low fine-particle fractions and significantly higher oropharyngeal deposition rates of up to 80%. In vitro aerosol measurements are frequently based on rudimentary throat models and do not forecast in vivo deposition **[**16]**.** Device limitations play a part in the problem; in particular, passive DPIs are unable to provide dependable performance when faced with substantial obstruction, and variations in resistance and feedback mechanisms lead to inconsistent delivery **[5].** The reproducibility that DPIs can attain in this regard is limited by a combination of drug excipient limitations, aerodynamic limitations, and user-device incompatibility.

6.4 patient Related Challenges: Inspiratory Flow Dependency and Technique Errors

DPIs are still mostly user-dependent, and clinical efficacy is influenced by inspiratory flow and technique. Up to 90% of patients will make at least one handling (or inhaler) error, usually because of poor preparation, exhaling before inhaling, or insufficient inspiratory effort [30]. Because they have less inspiratory capacity to implement optimal inhalation flow than others, children, older adults, and patients with advanced asthma are disproportionately affected by handling errors [5]**.** Because inter-device resistance varies, patients may misuse new inhalation devices even after receiving instruction. While instruction under ideal circumstances might reduce the frequency of handling errors, continuous training and feedback are essential because technique retention is still difficult and attrition rates are high.

6.5Emerging Technologies: Nanotechnology, Combination Therapies, and Personalized Inhalers

Particle engineering and nanotechnology are expanding and redefining DPI design to combat ongoing challenges. In addition to extending pulmonary residence, liposomes, polymeric nanoparticles, nanostructured lipid carriers, and other nanocarriers and cyclodextrin complexes also enhance aerodynamic stability and can transport delicate biomolecular medications, such as peptides and nucleic acids **[**31**].** PRINT® micromolding, particle engineering-excipient-enhanced growth, and porous microparticles have demonstrated the potential for dispersibility at inspiratory flows lower than has historically been feasible, though scaling and regulatory challenges still exist **[32]** doi: 10.1186/s40248-017-0092-5”**.** Combination treatment When corticosteroids, bronchodilators, or anti-infectives are co-administered as part of a fixed-dose regimen to ensure treatment adherence, DPIs can also be equally disruptive [33]. First, we need to clarify the use of newer technology, such as personalised inhalers created through CFD modeling, sensor-enabled feedback, or functional respiratory imaging (FRI) are used to tailor and enhance aerosolization based on each patient's unique inspiratory profile. [34]. First, we must make clear how more recent technologies, like sensor-enabled feedback, functional respiratory imaging (FRI), and customized inhalers made using CFD modeling, are used to tailor and enhance aerosolization based on each patient's unique inspiratory profile.

6.3 suggestions for future Research and Innovation

- Future studies on dry powder inhalers (DPIs) ought to go beyond merely improving their performance through small incremental changes, it should focus on developing new approaches with a n emphasis on patients and their needs.
- Finding biocompatible excipients that will enable us to control the moisture sensitivity of dry powder formulations and enhance the aerodynamic efficiency of these formulations and enhance the aerodynamic efficiency of these formulations is one of the highest priorities for future research in this area. Biocompatible excipients may include phospholipids, polymer with a nanostructured carrier and a high glass transition temperature (Tg). [31].
- Particle property manipulation is vital to obtain highly porous and large particle properties while ensuring optimal dispersion and stability of the powder formulation during the powder Excipient-enhanced growth and the freeze-drying technique [32**].**
- Adaptive DPI system designs will focus on the inspiratory capabilities of a user; thus, these systems must be developed with active aerosolization systems and airflow optimization through the used of computational Fluid Dynamics (CFD) [5].
- Integrating advanced and innovative technologies, including sensor-enabled DPI systems provides clinicians and patients with improved treatment outcomes by providing live monitoring monitoring of medication adherence, providing real-time user feedback and providing individualized doses [33].
- For advanced DPI systems to be clinically accepted there is a need to establish harmonised evaluation frameworks that include a coordinated evaluation of the in vitro- in vivo (IVIVC) correlation using current standards and establish coordination between regulatory agencies, clinical evaluations and evaluations of economic impact, [34].
- Lastly, next-generation DPIs will develop into accurate, safe, environmentally sustainable respiratory treatments with better worldwide accessibility if a systems-based approach that incorporates pharmaceutical science, engineering, digital health, and policy harmonization is adopted.

Conclusion

By utilizing developments in formulation science, delivery systems, and patient-sensitive delivery, dry powder inhalers (DPIs) have become a mainstay in the treatment of asthma. DPIs are established as a therapeutic delivery tool in the management of asthma, whether through particle engineering and excipient optimization for improvements in performance, stability, and deposition or increased clinical evidence showing DPIs are comparable or even superior in some situations to Nebulizers and pressurized metered-dose inhalers (pMDIs) (if appropriate devices are selected and patient training is embedded)**.** By utilizing developments in formulation science, delivery systems, and patient-sensitive delivery, dry powder inhalers (DPIs) have become a mainstay in the treatment of asthma. DPIs are established as a therapeutic delivery tool in the management of asthma, whether through particle engineering and excipient optimization for improvements in performance, stability, and deposition or increased clinical evidence showing DPIs are comparable or even superior in some situations to Nebulizers and pressurized metered-dose inhalers (pMDIs) (if

appropriate devices are selected and patient training is embedded). Future systems that use nanocarrier formulations, integrated delivery options, or digitally integrated DPIs that offer nano-aerosolized, precise dosing, and active real-time disease management are all exciting possibilities. These tool concepts, along with adherence systems, smart sensors, and precision aerosolization, will transform DPIs from their current use as a passive delivery method to an active platform for real-time disease management. Future research must incorporate strategies to start research, such as formulation-dispensing approaches, cost-effective regulatory approval, and safety-reproducibility-effectiveness, when considering the future and when DPIs will be widely approved, demonstrating the use of DPIs in providing patient-focused adherence and management paradigm. These management strategies will not only improve DPIs' standing within management strategies, but they will also aid in the development of the next generation of DPIs as the favoured modality.

List of Abbreviations

ACT- Asthma Control Test
ADPI- Active Dry Powder Inhaler
AFM- Atomic Force Microscopy
API- Active Pharmaceutical Ingredient
CFD- Computational Fluid Dynamics
CFC- Chlorofluorocarbon
DSC-Differential Scanning Calorimetry
DPI-Dry powder Inhaler
DPPC- Dipalmitoyl phosphatidyl choline
DVS-Dynamic Vapour sorption
FEV_1- Forced Expiratory volume in one second
FPF-Fine particle Fraction
FRI- Functional Respiratory Imaging
HA- Hyaluronic Acid
HPA axis- Hypothalamic -pituitary-Adrenals Axis
ICS- Inhaled Corticosteroids
ICH Q1A(R2)- International council for Harmonisation, stability testing of new drug substances and products
IgE- Immunoglobulin E
IL- Interleukin
IVIVC- In vitro- In vivo correlation
LABA-Long -Acting Beta-Agonist
L/min- Liters per minute
MDI/pMDI- (Pressurized) Metered Dose Inhaler
µm-Micrometre
Maillard reaction – non-enzymatic browning reaction between reducing sugars and amines
PEF/PEFR- peak Expiratory Flow/ peak Expiratory Flow rate
PIF- Peak Inspiratory Flow
PK (pk)-pharmacokinetics
PD- Pharmacodynamics
PLA- Polylactic Acid
PLGA- poly (lactic -co-glycolic acid)
PRINT®- Particle Replication in Non -wetting Temples
PROs- Patient -Reported Outcomes
PXRD- Powder x- ray Diffraction
RCT- Randomized Controlled Trial
SABA- Short -Acting Beta-Agonist
Tg- Glass Transition Temperature
Th2-T-helper Type2
TSLP- Thymic stromal Lymphopoietin

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