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Design, development, and technical considerations for dry powder inhaler devices

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The dry powder inhaler (DPI) stands out as a highly patient-friendly and effective pulmonary formulation, surpassing traditional and other pulmonary dosage forms in certain disease conditions. The development of DPI products, however, presents more complexities than that of other dosage forms, particularly in device design and the integration of the drug formulation. This review focuses on the capabilities of DPI devices in pulmonary drug delivery, with a special emphasis on device design and formulation development. It also discusses into the principles of deep lung particle deposition and device engineering, and provides a current overview of the market for DPI devices. Furthermore, the review highlights the use of computational fluid dynamics (CFD) in DPI product design and discusses the regulatory environment surrounding these devices.

Introduction

The pulmonary route for drug administration has a pivotal role in health care due to the extensive surface area of the lungs, which facilitates both local deposition and systemic delivery thanks to highly permeable nature and robust blood supply. This route is effective for the absorption of not only small therapeutic agents at the alveolar epithelium of the distal lung but also a range of macromolecules, including peptides and proteins.

Sagar Dhoble graduated from the Institute of Chemical Technology, Mumbai, India. His research work involves novel treatment modalities for infectious and non-infectious pulmonary disorders. It is primarily focused on the pulmonary delivery of nanoformulations for the treatment of lung disorders such as pulmonary hypertension and cystic fibrosis. He has an excellent academic record with several awards, among which a Bill & Melinda Gates Fellowship and a Tom Lantos Community Service Award for his work on pulmonary hypertension are highlights.

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When compared to oral administration, pulmonary delivery offers several key benefits: it circumvents first-pass metabolism, ensures swift absorption of drugs, and is subject to lower enzymatic activity, making it a more efficient route for drug delivery.[p1],[p2]

Chronic lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis, idiopathic pulmonary fibrosis (IPF), and pulmonary tuberculosis, represent a group of pulmonary disorders that are often fatal and lack effective treatments for restoring normal lung function.[p3] In response, several pulmonary drug-delivery systems have been developed to treat these prevalent conditions. Nebulizers, pressurized metered dose inhalers (pMDIs), and dry powder inhalers (DPIs) are among the most clinically used and researched methods for drug application, each offering distinct benefits and drawbacks. Nebulizers, for instance, require a compressed air source, whereas pMDIs necessitate propellants and face challenges that include sedimentation, crystallization, and high-velocity dosage elimination. DPIs, introduced to mitigate some of these issues, achieve enhanced physicochemical stability and deeper lung deposition by leveraging the patient's own respiration.[p4] These portable devices dispense powdered medications efficiently, requiring minimal synchronization between breathing and device activation. Easier to use and less irritating than pMDIs, DPIs combine micronized drug particles (1–5 μm) with larger carrier excipients (such as lactose, mannitol, or sorbitol) to create user-friendly powder blends. Compact and patient-compliant, DPIs do not need spacers and do not rely on patient breathing coordination, offering stability superior to that of aqueous solutions and eliminating the need for cold chain storage for thermosensitive products, which is especially beneficial in developing economies. DPIs also avoid the use of propellant gases such as chlorofluorocarbons (CFCs), which are harmful to the ozone layer. The powder form presents unique challenges, however, requiring optimal aerosolization characteristics and lung delivery profiles.[p5] Therefore, DPI formulation and device design are crucial for effective drug delivery to the lungs. The following sections will delve into the principles and significance of DPI device engineering for therapeutic lung delivery.

Biophysical principles of deep-lung particle deposition

The deposition pattern of drug particles in the lungs is influenced by several biophysical factors:

i) the aerodynamic characteristics of the particles (including size, true density, hygroscopic nature, shape, and electrical charge);
ii) the breathing pattern of the patient (considering aspects such as flow rate, volume of ventilation, and the duration of breath-holding at end-inspiration);
iii) the timing of aerosol pulse delivery within the respiratory cycle; and
iv) anatomical and morphological variations in the patient's airways.

The deposition of therapeutic aerosol particles on the respiratory tract walls is governed by three primary mechanisms: Brownian diffusion, which is the predominant mechanism for particles smaller than 0.5 μm; gravitational sedimentation, for particles larger than 0.5 μm; and impaction, which mainly occurs with particles larger than 5 μm. Other mechanisms that play a minor role in particle deposition are interception and electrostatic interactions between the particles and the lung walls.[p6],[p7],[p8],[p9]

Diffusion (Brownian motion)

Diffusion (Brownian motion) involves the random movement of aerosol particles in a gas, driven by molecular collisions. This leads to undirected motion, influencing their interaction with and eventual deposition on airway walls. This deposition is influenced by the diameter of the particles, with smaller particles having a greater probability of deposition in the lungs by diffusion and greater residence time in the respiratory tract, as given by Equation (1):

$$DEdif \quad t/d \tag{1}$$

where DE_{dif} is deposition efficiency by diffusion; t is residence time; and d is the diameter of the particles. The increase in residence time leads to increased collisions with gas molecules and hence increased deposition.[p10]

Sedimentation

Sedimentation occurs because of gravity, which is observed primarily in the narrow airways and alveolar cavities due to the narrow distance to be traversed by particles before they collide with the walls. The particles in the size range of 1–5 μm are mostly deposited by a sedimentation mechanism. Particle deposition by sedimentation is directly proportional to particle diameter or size and increases with a decrease in the size of airspaces. Therefore, particle deposition by sedimentation is greater in the alveoli than in the bronchi.[p8],[p11]

Impaction

Impaction occurs due to inertial forces acting on particles, and is largely dependent on particle size. Particles are deposited in both extrathoracic (nose, larynx) and intrathoracic (trachea, bronchi) areas. Deposition by impaction is influenced by the aerodynamic diameter of particles, airflow velocity, and airway structure. Larger particles (>5 μm) are more likely to be deposited due to greater inertia, whereas smaller particles (≈0.5 μm) are more likely to follow airflow streamlines, even in tortuous pathways.[p8],[p12]

Factors to consider when developing a new DPI delivery system

The effectiveness of inhaled drug delivery to the lungs hinges on the excellence of the inhalation device and formulation design. Technically, device and formulation engineering are the two major arms that play a crucial role in the effectiveness of the DPI delivery. Factors from both arms complement each other functionally and are entangled to contribute to the success of the DPI product. Hence, the DPI product development team is

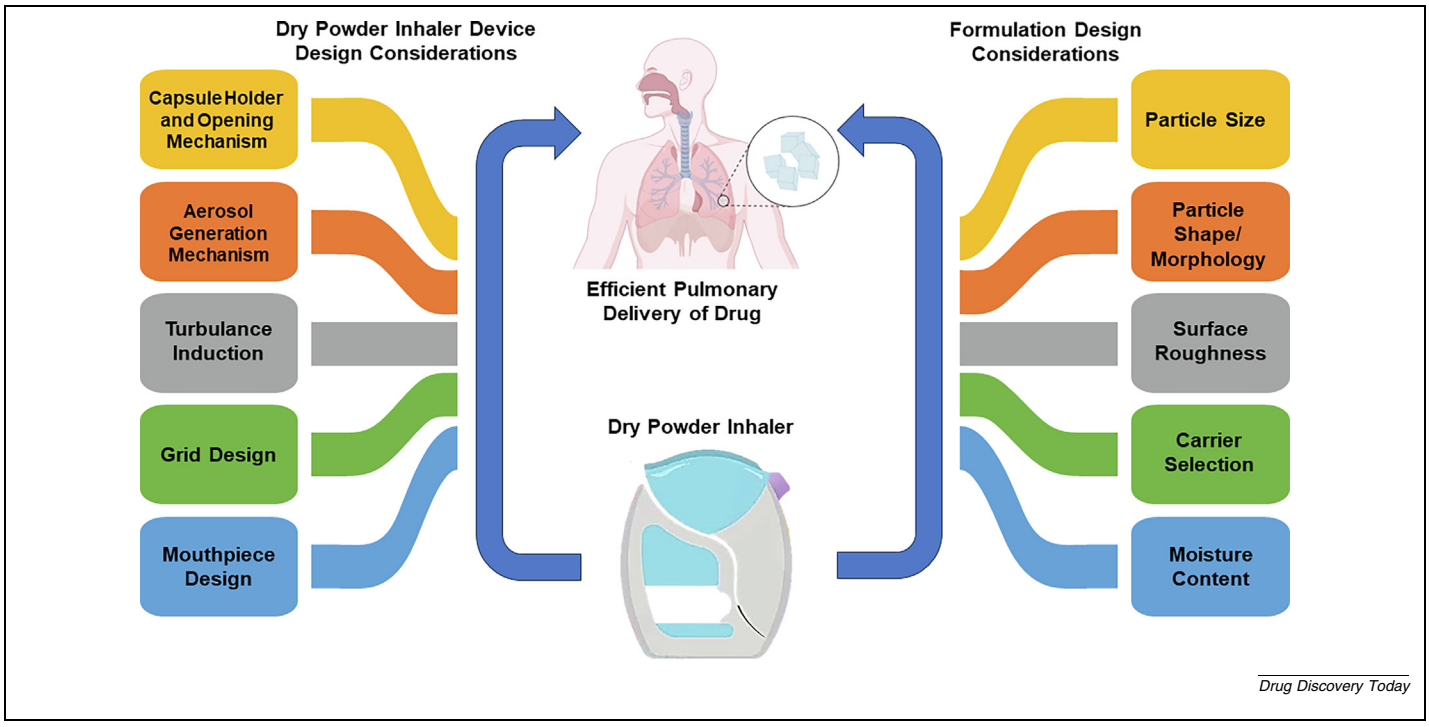

FIGURE 1

Factors affecting the dry powder inhaler drug delivery system. The right arm represents formulation-related factors such as particle size, particle shape, the surface roughness of particles, type of carrier, and the moisture content in the formulation; the left arm represents device-related factors such as the capsule-opening mechanism, the aerosol-generating mechanism, the turbulence mechanism inside the device, grid, and mouthpiece design.

mostly composed of a device engineering team and a formulation development team, each working in a closed environment but with interaction between the teams integral to the product development cycle. An optimal DPI product should be characterized by its portability, ease of use and cost effectiveness to the patient. It must accommodate multiple doses, safeguarding them against moisture, and should incorporate an audio-visual indicator for dose tracking. The device should consistently deliver accurate and reproducible doses throughout its lifespan, minimizing losses due to oropharyngeal deposition and exhalation, and should operate effectively across a spectrum of inspiratory flow rates. The formulation, which must be both physically and chemically stable, should have a particle size conducive to efficient delivery to the deep lung. Compatibility with various drug classes and dosages is essential, alongside minimal interaction between the drug and device components. At present, no market-available DPI product achieves all of these ideal characteristics. This gap drives ongoing research to enhance DPI functionality, addressing diverse challenges with varying degrees of innovation. Nonetheless, the proper training of patients in DPI administration and storage remains a critical aspect.[(p6),(p13)] The following section details the two arms of DPI development, device design and formulation design, which are instrumental in producing a marketable DPI drug delivery product (Figure 1).

Formulation factors impacting deep lung delivery via DPI

Particle size

The particle sizes of both the drug and the carrier critically influence DPI aerosolization. Research has shown that smaller particle sizes improve the respirable fraction of the drug delivered by DPIs. This comes, however, with trade-offs in dose uniformity and increased oropharyngeal deposition. The physical characteristics of carrier particles, such as their morphology, density, geometric diameter, and surface texture, are pivotal in fine-tuning aerosol particle size. Ooi *et al.*[(p14)] explored the impact of these aspects on DPI performance, uncovering enhanced aerosol efficacy. This improvement was attributed to a reduction in the number of drug particles that were attached to each carrier, an expansion in surface area, and increased interactions between carriers during aerosolization, along with the reduced particle size. In this scenario, drug release appears to be more influenced by the frequency and nature of collisions (frictional and rotational) among particles than by traditional momentum transfer. Moreover, carriers that exhibit a broad range of particle sizes (indicated by a high polydispersity index [PDI]) tend to form more diverse mixtures with the drug, potentially leading to more variable patterns of drug deposition in the lungs during inhalation.[(p15),(p16)]

Particle shape or morphology

The efficacy of aerosolized drug delivery to the deep lung is significantly influenced by the particle shape and morphology of the carrier. Variations in these aspects can result in different drag forces and terminal velocities during aerosolization, which subsequently affect deposition in the respiratory tract. Numerous studies have demonstrated the capability of carrier particles of specific shapes to deliver drugs effectively to the smaller airways, thereby enhancing lung drug deposition. In particular, low-density, pollen-shaped carrier particles have shown increased

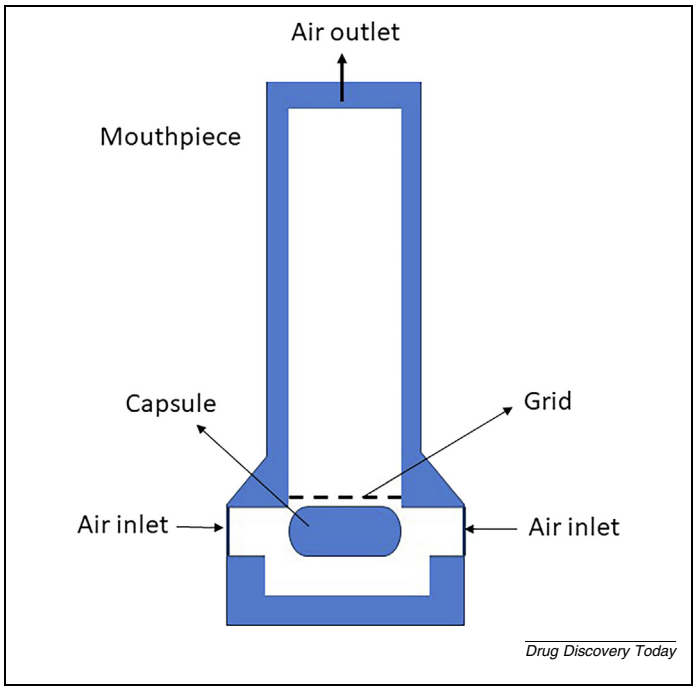

FIGURE 2
General design of a dry powder inhaler (DPI). An ideal DPI consists of a capsule holder, an air inlet mechanism, the grid and a mouthpiece outlet for powder delivery.

lung deposition, attributed to their prolonged drug-binding capacity. Key parameters for quantifying particle shape include elongation ratio (ER), flatness ratio (FR), roundness, shape factor (F shape), angularity, and surface factor (F surface). These are typically measured using scanning electron microscopy (SEM), optical microscopy, or other imaging methods.[p17],[p18] Kaialy *et al.*[p19] investigated the impact of carriers with diverse morphologies, focusing on the elongation ratio (ER) in aerosolizing salbutamol sulfate. Their findings highlighted that a higher ER led to improved efficiency of delivery to the lower airways. Nevertheless, this benefit is countered by challenges such as increased retention in the DPI device and throat resulting from higher ER.[p19]

ER and FR are especially crucial in estimating shape properties. ER assesses particle irregularity and elongation, with more elongated or irregular shapes, or rougher surfaces, resulting in higher ER values. FR indicates particle flatness, with a high FR corresponding to a flatter surface. Regular geometric shapes such as smooth spheres and perfect cubes display ERs and FRs of 1.

Particle shape irregularity is further delineated using second-order descriptors such as F shape and angularity. The F shape value, ranging from –1 to 1, denotes smoothness, with a value closer to 1 indicating a smoother particle, and lower values suggesting more irregularity or roughness. Angularity, conversely, is independent of ER. The F surface, a third-order descriptor, represents surface roughness, with a value of 1 indicating smoothness and lower values denoting roughness. F shape is unique as it is the only factor determined macroscopically; F surface and roughness are both ascertained macroscopically by examining surface texture. Another descriptor, S_{ree}, is utilized for a comparative analysis of surface smoothness across particles with varying ERs. This metric, which considers both F shape and ER, is computed by assuming a rectangular particle shape, which offers a nuanced understanding of particle surface characteristics.[p20]

Surface roughness

Formulation parameters significantly influence deep lung delivery, with surface roughness being a critical factor. Effective pulmonary drug delivery hinges on the ability of drug particles to adhere to and subsequently detach from carrier surfaces. The interaction between drug particles and carriers is largely determined by the surface contact area, which varies depending on the inherent surface roughness of pharmaceutical-grade DPI carriers. This roughness is categorized into three categories. First, particles featuring micrometer-scale topography offer extensive contact areas, leading to stronger adherence of micronized drug particles but resulting in reduced detachment efficiency. Second, nanometer-scale topographic carriers provide numerous drug binding sites, facilitating easier drug release during inhalation. Last, carriers with smooth surfaces exhibit less roughness, enhancing drug adhesion but complicating drug-carrier separation. Thus, nanometer-scale carriers are considered optimal for pulmonary DPI formulations because of their efficient drug binding and release dynamics.[p21] The impact of surface roughness on DPI aerosolization performance has, however, yielded varying results. For instance, Flament *et al.*[p22] observed that increased lactose surface roughness correlated with enhanced terbutaline sulfate adherence but decreased the fine particle fraction (FPF). FPF is the mass, or proportion with respect to the nominal dose, that falls within a size range considered sufficiently small to enter the lungs, usually representing the fraction of particles below an aerodynamic diameter size of 5 μm.[p22],[p23] Conversely, Kaialy *et al.*[p24] reported improved DPI performance with rougher lactose particles, resulting from reduced salbutamol sulfate adhesion. The interplay between surface roughness and aerosolization is attributed to the fact that greater roughness provides more points of contact for drug attachment to the carrier.[p24] To modulate surface roughness, techniques such as milling, coating dry powder mixing, and the addition of finer powders have been investigated. Tools such as atomic force microscopy, SEM, confocal microscopy, and transmission electron microscopy (TEM) are instrumental in providing direct measurements of surface roughness.[p25],[p26]

DPI device design and engineering

Capsule holder and opening mechanisms

In DPI device design and engineering (Figure 2), the capsule holder and opening mechanisms play a crucial role in the initial stages of drug delivery. The holder should securely contain the capsule during the process of opening or cutting, as this is crucial for efficient delivery. The act of opening creates an orifice, through which the powder is deagglomerated; a smaller orifice typically enhances this effect.[p27] The mechanism for opening must ensure complete and consistent powder delivery with each actuation.

Various methods are employed in DPIs for capsule opening:

Single unit-dose inhalers

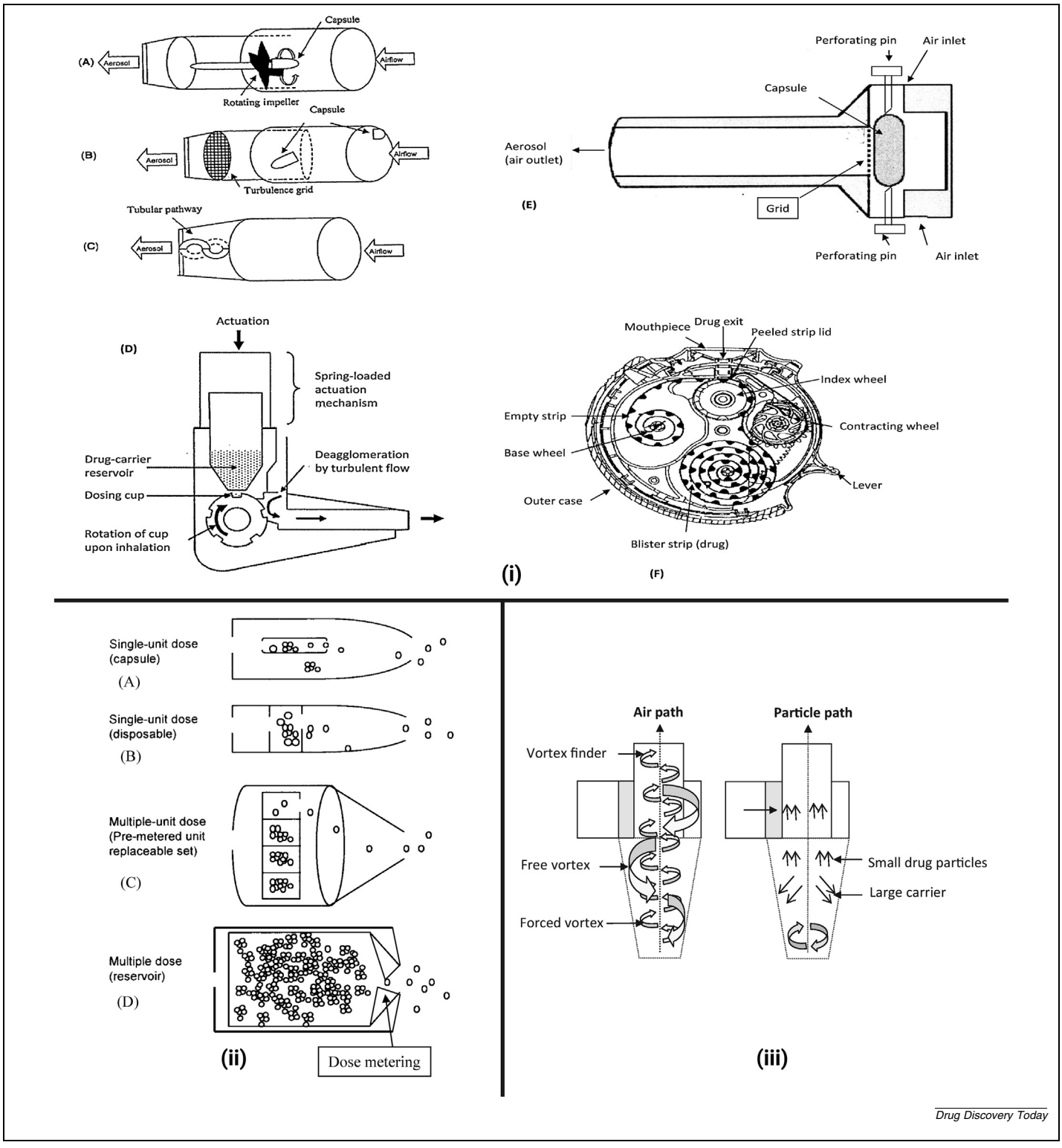

FIGURE 3

Properties of dry powder inhalers (DPIs). (i) Different types of inhaler devices with varying mechanisms for drug deagglomeration and dispersion A. Spinhaler®, B. Rotahaler®, C. Turbuhaler®, D. Easyhaler®, E. Aerolizer® and F. Diskus® inhalers. (ii) Different types of drug dose available in DPI formulations. (iii) The reverse flow cyclone mechanism for deagglomeration. (Adapted from Islam and Cleary.38).

- Spinhaler® employs a piercing technique. At high flow rates, both the impeller and the capsule experience vibrations from the inhaled air, leading to mechanical fluidization. This is supplemented by capillary fluidization due to the pressure differential across the capsule, which allows powder discharge along the capsule walls and out through the perforations.

Concerns about uneven orifice shapes and capsule material flaps that might close upon inhalation are mitigated by studies indicating that these factors do not affect the uniformity of powder release.[p28],[p29]

- Rotahaler®, a breath-actuated device, splits the capsule into halves upon rotation of the device base, subsequently releasing the powder. Patients inhale deeply to deposit the powder into the respiratory tract.[p30]
- Inhalator Ingelheim, a single-capsule device, pierces the capsule upon pressing a button. The powder is released through capillary fluidization due to the significant pressure gradient, and vibration of the capsule in the airstream aids in emptying it.[p31]

Multiple unit dose inhalers

- Turbuhaler® contains a reservoir of up to 200 doses of micronized, undiluted, and loosely aggregated drugs. The device operates by twisting the base, which dispenses the drug onto a rotatable disk with fine orifices in the dosator. Excess powder is scraped off, and a metered dose is delivered into the inhalation channel when the grip is twisted, propelled by the turbulent airflow generated during patient inhalation.[p32]
- Asmanex Twisthaler® is designed to deliver mometasone, an inhaled corticosteroid, after the cap is removed by twisting the colored base counterclockwise. This action loads a single metered dose, which is inhaled through the device with the aid of turbulent airflow, as is the case for Turbuhaler®.[p33]
- Diskhaler® is a multidose inhaler featuring a Rotadisk, a rotatable disk-shaped blister pack containing 4–8 unit doses. Folding the hood punctures the blister pack, releasing the formulation for inhalation.[p33]
- Diskus® is a multidose inhaler that houses 60 doses in pockets on a foil strip. Each dose is exposed and released by peeling off the foil, with the used blister and lid foils being collected inside the device for disposal.[p34],[p35]
- Easyhaler® contains 200-unit doses of a lactose-drug blend. Its metering mechanism relies on gravity, assisted by shaking, to transfer formulation from the receptacle to the metering cylinder. Depressing the overcap rotates the cylinder, releasing a powder dose into the mouthpiece.[p36]

TABLE 1

Aerosol dispersion mechanisms for the dry powder inhaler.

Mechanisms	Inhaler	Manufacturer
Venturi effect	Easyhaler®	Orion
Impact bodies	Clickhaler®	Innovate Biomed
	Certihaler®	SkyePharma
Discharge channels	Turbuhaler®	AstraZeneca
	Twisthaler®	Schering Plow
Cyclone chambers	Pulvinal®	Chiesi
	Airmax®	Ivax
	Novolizer®	Viatris
	Taifun®	LAB International (formely Focus Inhalation)
Pressurized air	Inhance®	Nektar
	Aspirair®	Vectura
Battery-powered	(Inhaler names not yet released)	Microdose Technologies

These mechanisms highlight the intricate engineering behind DPIs, which ensure effective and consistent drug delivery (Figure 3).

Aerosol generation mechanisms

In inhalation devices, the interplay between the fluidized powder and solid powder phases is critical for powder movement (Table 1). The aerosolization of a powder is assessed through its static properties, dilation, fluidization, and deagglomeration. Fluidization, the dispersion of bulk dry powder upon contact with air molecules, can occur through aerodynamic methods (such as shear force, gas assistance, or capillary action) or through mechanical means (such as vibration and impaction).

The subsequent stage, deagglomeration, involves the interaction of the fluidized powder with air, leading to the separation of drug particles from their carriers, which results in the formation of primary respirable particles. This stage is facilitated by turbulent shear and inertia-driven mechanisms such as vibration, collision, and centrifugation.

The relationship between the dispersed particles and the dispersing medium has been explored both theoretically and empirically. Forces such as rapid acceleration and deceleration, as well as turbulent eddies, impact loose aggregates in the medium. The dispersion process in powder-fluid interactions includes shear-assisted dispersion or dispersion due to rapid velocity changes, impact, and a mechanical dispersion mechanism (such as fluidization, mixing, vibration or scraping).

Aerosolization employs these methods in three phases: i) delivery, in which the powder begins to move into the dispersing element, often in a vibrating container; ii) dispersal/entrainment of the aggregates with no effect on the primary particles; and iii) transport and presentation, during which the powder is moved to a specific delivery region.[p15]

The air-conducting components of DPIs must coordinate with the device's air inlets and outlets for effective deagglomeration, maximizing lung delivery and minimizing oropharyngeal and device deposition. The duration, nature, and intensity of the forces that are applied during this process define the particle deagglomeration pattern. Prolonging deagglomeration in the chamber enhances mouthpiece delivery. Inertial forces such as collision, vibration, and centrifugation detach particles from carriers. An air classifier, combined with these forces, can improve particle deagglomeration, but complete powder release from the capsule is vital to prevent drug loss. Despite the complicated design of a DPI, an air classifier and its associated whirling chamber are crucial for effective aerosolization.[p5]

Induction of turbulence. DPIs have three main components: an air inlet, a powder receptacle, and a formulation delivery port. Effective aerosolization of the dose from a static powder bed is hindered by normal air currents due to insufficient shear forces. When aerosolized, a particle encounters two force types: body forces (which act through gravity and electromagnetism, impacting the mass of the particles) and surface forces (force per unit area, including shear stress and tangential stress, which is crucial for powder deagglomeration). Turbulent flows in DPIs are highly asymmetric, characterized by high velocities and intense eddies, which subject drug particles to multidirectional shear stress. This turbulence, which is crucial for deagglomerating particles, is

often induced using spiraling channels in inhalers such as the Turbuhaler®. It enhances the surface area of flow channels and increases device-particle deposition. Recent DPI designs, such as the NEXT® DPI, create an energized cyclone within a cylindrical receptacle featuring tangential inlets. Computational fluid dynamics (CFD) tools have been employed for design optimization, notably in removing 'dead spots' of drug deposition. Another innovative design is the Conix® inhaler, which utilizes reverse cyclone technology. During inhalation, a vortex forms within the cyclone chamber. Air descends the cyclone, halts at the bottom, and reverses direction, exiting through a circular outlet. This mechanism efficiently manages airflow and drug delivery.[p37]

Mechanical forces. The mechanical forces that are essential for powder deagglomeration in inhalers are generated using various mechanisms. For instance, the Spiros® inhaler employs a battery-operated impeller to aerosolize the powder in the flow stream. In another approach, a turbine activates the impeller during inhalation in a passive DPI, as outlined in US Patent No. 6237591. In addition, low-density beads in the dispersion chamber (US Patent No. 6971384) assist in mechanical deagglomeration. Upon inhalation, the powder traverses the chamber, where it undergoes deagglomeration due to interparticulate colloidal and particle–wall interactions. Moreover, in US Patent No. 5655523, a spring-driven hammer mechanism is utilized to deagglomerate powder doses. Another solution uses baffles (US Patent No. 5724959) to create mechanical forces without adding complexity. These devices feature a narrow channel downstream of the powder chamber, leading to a larger volume chamber with an impactor plate. This setup induces a sudden flow path alteration. Larger carrier particles, with a longer stopping distance, are directed towards the periphery, undergoing impaction and detaching the drug from the carrier. The impactor plate's width and positioning are crucial for determining particle size cut-off.[p38] Mechanical force-based inhalers, though more intricate and failure-prone due to their moving components, offer a potential alternative to turbulence-driven devices.

Pneumatic forces. Pneumatic forces, generated primarily through compressed gases, are a fundamental mechanism in modern drug delivery systems. Notably, designs often incorporate a manual pump or an external air compressor that compacts air within a device (exemplified in US Patent Nos 5875776 and 5775320). A prime example is the Nektar® Pulmonary Inhaler, initially known as the Inhale DPI (Inhale Therapeutic Systems, US Patent No. 6257233). This inhaler features a dual-chamber mechanism: the lower compression chamber generates compressed air, whereas the upper chamber retains the aerosolized powder post-actuation. The inhalation process involves circulating compressed air through the powder bed, effectively transporting the powder into the upper chamber for patient inhalation. Another innovative design is the Vectura Aspirair®, which utilizes a manually compressed air bolus to disperse the powder during inhalation. Similarly, the Prohaler®, a multidose powder inhaler, employs a pump that delivers compressed air for metered doses, thereby enhancing powder dispersion. This air-assisted fluidization reduces dependency on inspiratory flow, ensuring efficient particle dispersion.

Vacuum-based aerosolization, delineated in US Patent No. 6138673, introduces an alternative pneumatic dispersion technique. In this method, a vacuum created in the DPI chamber assists in aerosolizing the formulation. The device's design allows for a variable chamber volume, which generates a vacuum when manually actuated. Ambient air enters through a valve in response to the trigger, passing through the dose receptacle to aerosolize the drug.[p39]

Synthetic jetting technology, described in US Patent No. 7334577, is another approach to generating pneumatic forces for powder dispersion. This technology involves a wave-generating device and a rigid wall with an orifice at opposing ends of a chamber. High frequency and amplitude acoustic waves from the generator create a directed air stream. This synthetic jet, consisting of vertical air puffs synchronized with the generator's frequency, can utilize a piezoelectric component or an electrodynamic transducer. Upon activation, high-frequency oscillations aerosolize the dry powder formulation in the jetting compartment. The synthetic jet then expels the aerosolized powder from the chamber into a delivery passage for patient administration.

Vibration-induced dispersion in inhalers. DPIs that utilize capsules for pre-metered dose delivery rely on mechanical vibrations to deagglomerate the powder. The Handihaler®, an example of such a DPI, generates rapid oscillations of the capsule. As the patient inhales, air flows through a narrow tube and into a larger capsule chamber. This airflow expansion creates a turbulent eddy in the middle region as a result of air recirculation, which, in turn, oscillates the capsule. The Handihaler® employs this vibration to deliver the dose effectively.[p27]

Another DPI type operates on a passive aerodynamic 'flutter' principle (US Patent No. 11713180). Here, when an aeroelastic object is exposed to airflow, it vibrates. Positioning a powdered dose on an aeroelastic film enables effective aerosolization at low threshold flow rates.

Piezoelectric dispersion. Discovered by the Curie brothers in 1880, the piezoelectric effect involves the emission of electrical signals by anisotropic crystals when under stress. This effect is harnessed in DPIs through the triggering of rapid crystal vibrations by oscillating electrical potentials. Piezoelectric polymers, which are widely used in various applications, also facilitate DPI aerosolization. In the microdose inhaler illustrated in Figure 4 (US Patent No. 6026809), a piezoelectric vibrating mechanism contacts the drug formulation blister. As the patient inhales, an airflow sensor activates the piezoelectric element, causing the formulation to be dispensed through blister openings.

Similarly, Oriel Therapeutics, Inc.'s multidose inhaler (US Patent No. 6889690) uses a piezoelectric polymeric material for the powder-containing blisters. Inhalation triggers an electric supply to the blister, inducing polymer vibrations and dispensing the dose. Both examples represent active devices that require an external power source for piezoelectric activation.[p40]

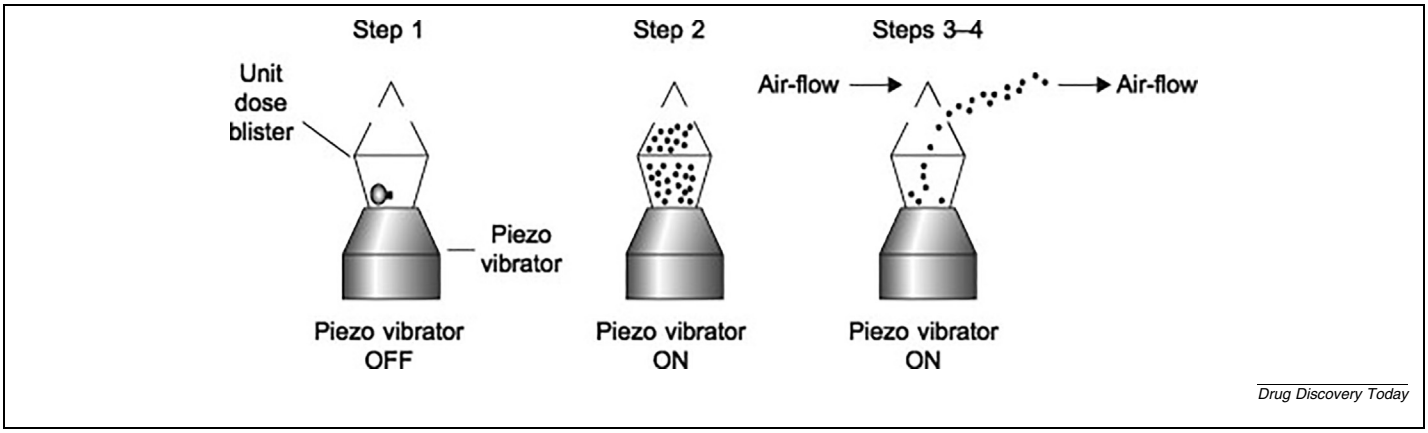

FIGURE 4

The Microdose® inhaler. This active inhaler uses an external source of piezoelectricity for dry powder dispersion and is minimally dependent on patients' inspiratory airflow, making it suitable for children and elderly patients. (Adapted from Preedy and Prokopovich.[p62]).

Electric and magnetic fields. Electric and magnetic fields offer unique mechanisms for deagglomerating micronized powder particles, leveraging the high charge-to-mass ratios of these particles. For instance, US Patent No. 6089227 details a DPI device that employs an electric field for this purpose. This device comprises dual chambers separated by a barrier housing a rotating dosing drum. One chamber holds the drug formulation, and the other connects to an air inlet and outlet. The drum, which is partially exposed to each chamber, attracts the charged powder particles when an electric field is applied. As the drum rotates, the particles detach in the opposite chamber in synchrony with the patient's inhalation, thereby delivering the dry powder formulation effectively.

Another invention, US Patent No. 6328033, utilizes an oscillating electric field to agitate the powder in a reservoir, facilitating its entrainment. During inhalation, this field, coupled with the airflow, ensures targeted delivery. This device also incorporates a magnetic field-based mechanism. Here, magnetic core particles coated with the dry powder are vibrated by an oscillating magnetic field, dislodging the powder for inhalation. Simultaneously, the continued magnetic field during inhalation confines these magnetic particles within the device, optimizing drug delivery.[p41]

Mouthpiece design

In designing the mouthpiece of a DPI, patient ergonomics are paramount, enabling both ease of handling and the ability to channel swirled particles effectively. Most inhalers adopt a rounded or semi-rounded design, ensuring a comfortable and secure fit in the patient's mouth. Although the size of the air channel in the mouthpiece has been found to have minimal impact on particle dispersion and *in vitro* lung deposition, the cross-sectional area is critical for formulation delivery. A larger cross-sectional area tends to decrease particle velocity, subsequently reducing particle deposition in the oral cavity. It is essential that the mouthpiece is seamlessly integrated with the device's deagglomeration mechanism and air channels for efficient formulation delivery.[p37],[p42],[p43]

The grid

A key component in many capsule-based DPIs is a grid, mesh, or screen, situated between the powder reservoir and the outlet. This element plays a crucial role in preventing broken capsule fragments from entering the patient's oropharynx, thus mitigating local irritation or inhalation blockage. However, the presence of a grid can diminish the tangential airflow components, potentially leading to powder retention within the mouthpiece. The grid aids in particle deagglomeration through powder impaction and aligns airflow exiting the whirling chamber. Consequently, the grid or screen significantly influences device performance by altering the airflow pattern both before and after its location. A specific study exploring the influence of the grid inside the Aerolizer® DPI compared three different grid designs (one original and two with increased porosity). Findings indicated that the Aerolizer® grid acts as a turbulence suppressor, reducing tangential flow within the device.[p44],[p45]

Application of CFD in DPI design

CFD employs numerical analysis, data structures, and computer simulations based on fluid mechanics to solve problems related to fluid motion. CFD is instrumental in allowing medical researchers to examine body fluid dynamics and to enhance biomedical device research and development. It employs various models such as direct numerical simulation (DNS), Reynolds-averaged Navier Stokes (RANS), and large eddy simulation (LES) to simulate aerosol and DPI device performance. DNS offers high accuracy but at prohibitive computational costs. RANS, which is used in practical applications such as inhaler design, simplifies the governing equations and is cost-effective but loses some accuracy due to its time-averaged nature. LES models, though more accurate, require significantly more computational power.[p46] The application of CFD in DPI development is complex due to the interrelated processes of powder aerosolization, deaggregation, and aerosol dispersion. Predicting aerodynamic and adhesive forces in fine powders is difficult due to their irregular shapes and surfaces, which complicate our understanding of DPI powder aerosolization and delivery. The complexity

TABLE 2

Examples of computational fluid dynamics models used for DPIs.

Title of the study	Conclusive results obtained	Reference no.
Estimating inter-patient variability of dispersion in dry powder inhalers using CFD-DEM simulations	The study highlighted the effect of consideration of variable flow rate profiles instead of constant flow rate on the modeling of air flow and carrier particle motion in a capsule-based dry powder inhaler. This emphasized the clearer view on considering patient profile based flow rate during the simulation studies which can display better view on the carrier particle motion in the device.	(p50)
Capsule-Based dry powder inhaler evaluation using CFD-DEM simulations and next generation impactor data	An empirical approach with the combination of CFD and discrete element method (DEM) model was used to understand the impact of drug/excipient adhesion forces and the DPI resistances on the aerosol performance. The study indicated that the aerosol performance is excellent when the low resistance device was paired with formulations that exhibit low API/excipient adhesion and vice versa.	(p51)
A CFD-DEM investigation of powder transport and aerosolization in ELLIPTA® dry powder inhaler	This study simulated the fluidization, deagglomeration and transport of carrier and API particles in a commercial ELLIPTA® inhaler in two inhalation profiles that are representative of moderate asthma and very severe COPD patients, and three different mouthpiece designs. The study revealed maximum effect of air-carrier and carrier-carrier interaction on FPF while its minimum for carrier wall interactions.	(p52)
Dry Powder Inhaler Device Influence on Carrier Particle Performance	Overall, it was found that a way to significantly enhance aerosol performance can be by matching the physical properties of formulation particles to that of the predominant deaggregation mechanism. Impaction was concluded to be a major deagglomeration mechanism in Aerolizer® based on its dependence on carrier particle size.	(p53)
Effect of device design on the in vitro performance and comparability for capsule-based dry powder inhalers	It was shown using the model that the tangential air inlet in the device produces a largely cyclonic airflow pattern. Large differences were observed in the performance of modified Cyclohaler® designs & the Handihaler®, pointing to the fact that it is not possible to simply attain comparable *in vitro* performance by matching of specific resistance of the test & reference products.	(p54)

increases with the presence of mechanisms such as deagglomeration, particle-device collisions, and airflow-induced forces. The impacts of individual forces on deagglomeration, which are influenced by powder properties and device design, remain unclear.(p47),(p48)

A landmark CFD study by Coates *et al.*,(p49) published in 2006, analyzed the Rotahaler® and Aerolizer® inhalers, highlighting the impact of design elements on their performance. It revealed that device design properties, such as grid structure, mouthpiece geometry, capsule size, and air-inlet size, significantly influence DPI performance, affecting aspects such as flow turbulence, particle impactions, and fine particle fraction (FPF). The study determined that a flow rate of 65 L/min optimizes FPF, throat deposition, and capsule retention. The study did not, however, model particle deagglomeration, limiting its ability to predict interparticular collision frequencies and intensities. Despite this, it offered valuable insights into the role of DPI device design in determining performance.(p49)

Numerous research efforts have employed CFD to provide an enhanced understanding of airflow and deagglomeration in DPIs. Table 2 presents a selection of CFD models that have been applied to aid the design of DPIs.

Although airflow dynamics within DPIs have been the focus of extensive CFD analyses, research on deagglomeration processes remains limited. Discrete element modeling (DEM) offers a method to simulate particle interactions and wall contact, using Newtonian motion equations to predict the movement and rotation of discrete particles, which are influenced by both contact and non-contact forces. DEM provides intricate insights into particle trajectories and the forces at play between them. When integrated with CFD, DEM facilitates highly precise predictions of particle interactions and movement, thereby offering an advanced approach to examine particle deagglomeration mechanics(p50),p(51),p(52),p(53),p(54).

In a study by Tong *et al.*,(p55) the mechanics of powder deagglomeration during mechanical impaction were explored, validating experimental findings. The key factors that were identified as affecting deagglomeration included particle–particle tensile strength and particle–wall impact energy.(p55)

Particle size and flow velocity were found to be interrelated; higher velocities led to more effective dispersion of smaller particle aggregates. Interestingly, particle size distribution had a less pronounced effect on dispersibility, with agglomerates that had narrower size distributions demonstrating better dispersion. Another investigation by the same team revealed that deagglomeration primarily occurs due to particle–wall impact, where fragmentation is determined by impaction energy and agglomerate strength. Turbulence appeared to be less influential, with powder deposition depending on impact angle and fragment inertial energy. These findings emphasize the importance of device design and flow conditions in achieving optimal dispersion, a conclusion supported by additional research using an Aerolizer®.

TABLE 3

Pharmaceutical development studies for inhalational products (Adapted from Reference no.[p59]).

Pharmaceutical development study	Pressurized Metered Dose Inhalers	Dry Powder Inhalers		Products for nebulization		Nonpressurized Metered Dose Inhalers
		Device-Metered	Pre-Metered	Single-dose	Multidose	
Physical characterization	Yes*	Yes	Yes	Yes*	Yes*	Yes*
Minimum fill justification	Yes	Yes	Yes	Yes	Yes	Yes
Extractables/Leachables	Yes	No	No	Yes	Yes	Yes
Delivered dose uniformity & fine particle mass through container life	Yes	Yes	Yes	No	No	Yes
Delivered dose uniformity & fine particle mass over patient flow rate range	No	Yes	Yes	No	No	No
Fine particle mass with spacer use	Yes	No	No	No	No	No
Single-dose fine particle mass	Yes	Yes	Yes	No	No	Yes
Particle/droplet size distribution	Yes	Yes	Yes	Yes	Yes	Yes
Actuator/mouthpiece deposition	Yes	Yes	Yes	No	No	Yes
Drug delivery rate and total drug delivered	No	No	No	Yes	Yes	No
Shaking requirements	Yes	No	No	Yes	Yes	Yes
Initial & repriming requirements	Yes	No	No	No	No	Yes
Low-temperature performance	Yes	No	No	No	No	No
Performance after temperature cycling	Yes	No	No	No	No	Yes
Effect of environmental moisture	Yes	Yes	Yes	No	No	No
Robustness	Yes	Yes	Yes	No	No	Yes
Delivery device development	Yes	Yes	Yes	Yes	Yes	Yes
Preservative effectiveness/efficacy	No	No	No	Yes**	Yes**	Yes**
Compatibility	No	No	No	Yes	Yes	No

* For suspensions.

** If a preservative is present.

This study found that inhaler performance is flow-dependent, with increased flow rates enhancing dispersion but also elevating powder retention within the device. These insights have been pivotal in advancing the understanding of DPI deagglomeration, a topic that had previously yielded inconsistent results in CFD studies.[p56],[p57]

Regulatory considerations in the development of DPIs

The development of inhalational products, such as pMDIs, DPIs, and nebulizers, is governed by guidelines from both the U.S. Food and Drug Administration (FDA)[p58] and the European Medicines Agency (EMA) (Table 3).[p59] Classified as drug–device combination products under 21 CFR 3.2(e), pMDIs and DPIs are subject to the stringent Current Good Manufacturing Practices (cGMP) for both drugs and devices (21 CFR part 4). A crucial aspect of these guidelines is design control (21 CFR 820.30), which mandates the demonstration of a lack of adverse interactions between the drug and device components, ensuring that their combined use is safe and effective. The FDA's guidelines for the pharmaceutical industry encompass product design and development processes, advocating for Quality by Design (QbD) principles. Concurrently, the EMA's guidelines articulate the clinical documentation necessary for orally inhaled products. This documentation includes requirements for both single active pharmaceutical ingredient (API) and combination products, particularly in extending market authorization. These guidelines aim to establish therapeutic equivalence between products that are intended for the management and treatment of conditions such as asthma and COPD.[p58],[p59]

Navigating the stringent criteria set by the FDA makes the acquisition of approval for generic drugs in the US market post-patent expiration a complex endeavor. From a formulation perspective, the generic product must mirror the reference listed drug (RLD) in terms of being an identical dosage form with the same active ingredient. The QbD methodology is typically recommended for determining excipient concentrations in generic formulations. This approach mandates equivalence in all *in vitro* assessments, and in pharmacokinetic and pharmacodynamic studies. *In vitro* evaluations encompass studies of single actuation content (SAC) and aerodynamic particle size distribution (APSD). In addition, device handling characteristics and resistance to airflow should be consistent between the generic and reference product devices. Regulatory guidelines detail the chemistry, manufacturing, and control aspects that are advisable for inclusion in new drug applications (NDAs) and Abbreviated New Drug Applications (ANDAs). These principles extend beyond initial approvals, being applicable throughout the clinical trials and the entire product lifecycle, as per the 2018 US FDA guidelines.[p58] In India, although there are no explicit guidelines for orally inhaled products, generic drug submissions must comply with the Central Drugs Standard Control Organization (CDSCO)'s "*Guideline for Bioavailability and Bioequivalence Studies*".[p60],[p61]

Conclusions and future perspectives

The delivery of drugs to the lungs through DPIs presents a promising avenue for achieving optimal therapeutic outcomes as they are highly effective. DPIs have become the favored option

for administering drugs to the lungs, owing to their patient-centric design and superior efficacy in specific medical conditions when compared to traditional dosage forms. Traditionally used mainly for the treatment of COPD and other chronic diseases, DPI devices have widened their scope to include the treatment of systemic and infectious diseases. The present review highlights the concepts of deep lung particle deposition and the factors to be considered while designing DPI devices. In addition, we have emphasized the distinctive device engineering and formulation parameters predominantly associated with the development of DPI products. We have also elaborated on the utilization of CFD in the design of DPI devices, discussing how these models can provide significant knowledge to improve the performance in clinical settings. Furthermore, we have considered the regulatory framework for DPI devices, recognizing the significance of complying with regulatory requirements in the process of developing and marketing DPI products.

In conclusion, DPIs have immense potential for the delivery of drugs through the pulmonary route. These drugs may be effective either locally or systemically, and may be used to treat both chronic and acute conditions. The emergence of new device technologies, particle engineering approaches, and better, modified excipients are paving the way for the development of increasingly effective DPI products.

Declarations of interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Sagar Dhoble: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Archana Kapse:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Vaibhav Ghegade:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Manasi Chogale:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Vinod Ghodake:** Writing – review & editing, Formal analysis, Data curation. **Vandana Patravale:** Writing – review & editing, Supervision, Conceptualization. **Lalitkumar Vora:** Visualization, Supervision, Resources, Writing – review & editing.

Data availability

No data was used for the research described in the article.

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