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Review Article

Nanotechnology Approaches Based DPI Formulations: Emerging Trends in Targeted Lung Delivery

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ABSTRACT

Due to its large surface area, thin epithelial barrier and extensive vascularization the pulmonary route has become an essential platform for both local and systemic drug delivery. Dry powder inhalers (DPIs) are unique among available devices because they are non-invasive propellant-free systems that enhance deep lung deposition patient compliance and drug stability. Polymeric nanoparticles, solid lipid nanoparticles, liposomes, proliposomes, lipospheres and nanostructured lipid carriers are examples of nanotechnology advancements that have improved bioavailability sustained release and targeted delivery. Powder flow dispersion and stability are further optimized by engineered excipients such as lactose, mannitol, trehalose, leucine and trileucine. Aerodynamic properties can be precisely controlled through the use of manufacturing techniques such as micronization, spray drying, spray freeze drying and supercritical fluid processing which are backed by Quality by Design (QbD). Notwithstanding these developments there are still issues: dose variability brought on by patient effort during inhalation sensitivity to moisture restricted regulatory approval of new excipients challenges with scaling up and a lack of knowledge regarding the long-term pulmonary safety of nanocarriers. To fully achieve the therapeutic potential of DPIs enabled by nanotechnology these gaps must be filled through translational research regulatory harmonization and integrated device–formulation design.

INTRODUCTION

For centuries pulmonary routes have been used to treat a variety of respiratory conditions. Balsams, myrrh, aromatic plant vapors and plant leaves were all used in ancient inhalation treatments. In the 1920s a nebulizer solution of adrenaline was introduced. In 1925, nebulizer insulin for pigs was used in diabetes experiments and in 1945 the recently discovered penicillins through pulmonary delivery was examined. Nebulizers were widely used and steroids had been introduced in the middle of the 1950s to treat asthma. The pressured metered dose inhaler (pMDI) which was first

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introduced in 1956 has emerged as the cornerstone of asthma treatment. Because of its special qualities which include a large absorptive area of up to 100m2 an extremely thin 0. 1 µm - 0. 2 µm absorptive mucosal membrane and a good blood supply this route has become more and more important in recent years. Nebulizers dry powder and pressurized metered dose inhalers are the three platforms on which devices based on these three platforms deliver drugs via the pulmonary route.[1]

A drug effectiveness is mostly determined by its intrinsic qualities and the particular illness it is intended to treat. A localized approach is made possible by inhaling the drug directly into the lungs which can lower the body`s overall medication concentrations and the need for larger dosages. This approach can produce notable therapeutic effects as numerous studies have shown and it may improve medication efficacy while reducing systemic toxicity. A decrease in fibrosis and other pulmonary complications has also been linked to the inhalation-based administration of these agents. Intranasal or oral inhalation routes are used to deliver medication to the lungs. Regardless of the delivery method the device drug formulation and the subject inhalation technique can all affect how effective nasal delivery is. Intra-tracheal instillation also known as intra-tracheal inhalation is the term used to describe the oral inhalation of medications.[2]

Therapeutic agents particularly synthetic biomolecules like proteins peptides and nucleic acids can now be delivered to the lungs using DPIs a revolutionary platform. A few of the special benefits of the pulmonary route are systemic delivery of biomolecules with high bioavailability and direct access to the lungs vast surface area and vascular network which allow for the local treatment of respiratory disorders. DPIs provide a non-invasive patient-friendly substitute for conventional parenteral routes in the administration of biomolecules by avoiding their disadvantages which include patient discomfort infection risk and low compliance. DPIs are non-invasive drug delivery methods that specifically target the respiratory system avoiding first-pass metabolism in the liver and gastrointestinal breakdown. Because of this they are an essential substitute for injectable and oral treatments especially for delicate biomolecules like proteins peptides and nucleic acids. By ensuring both localized and systemic therapeutic effects DPIs improve patient comfort and efficacy.[3]

Lung infections, cystic fibrosis, asthma and chronic obstructive pulmonary disease are among the respiratory disorders it is used to treat. Compared to conventional oral and intravenous medication IDP administration has a number of benefits such as increased compliance decreased systemic, side effects, and enhanced bioavailability.[4] It is versatile delivery systems which may require some degree of dexterity to operate, although one of the objectives of recent developments has been to simplify their operation. Typically, they dispense a metered quantity of powder in a stream of air drawn through the device by the patient own inspiration. In the design of a new powder inhaler consideration must be given to optimising the formulation of the powder containing the drug substance to ensure a chemically stable and consistent dose; design of the metering system within the inhaler to provide consistent doses over a range of inhalation conditions; and design of the powder inhaler itself to produce a convenient device that is comfortable and easy for the patient to use.[5] By using the patients own respiration DPIs improved physicochemical stability and deeper lung deposition. Larger carrier excipients (like lactose mannitol or sorbitol) are combined with

micronized drug particles (1–5 mm) to create DPIs which are easier to use and less irritating than pMDIs. powder blends that are easy to use.[6]

DPI provide few of benefits that is Encapsulating capability, long-term stability, no liquid propellant, no hand-lung inhalation coordination, altered pharmacokinetics, an extended release profile, enhanced tolerability, decreased toxicity, ease of use and noninvasiveness. The DPI devices are further divided into passive and active devices according to the mechanisms of particle dispersion and aerosolization. The energy needed for powder dispersion in a passive DPI device is provided by the patient inspiratory flow. Overdosing or underdosing may result from variations in the patient inspiratory flow which can also affect the amount of medication administered. The inspiratory flow of a patient is not a determining factor for an active DPI device.[7] Conventional inhalable formulations typically have large spongy grains vehicle-admixture particles etc. The microsized drug particles dissolve in the fluid inside the lungs when patients use traditional forms of inhalable powder formulation which DPI can overcome this.[8]

A thorough summary of nanotechnology-based approaches in dry powder inhaler (DPI) formulations for targeted pulmonary drug delivery is given in this review. It highlights how the incorporation of nanoparticles can improve therapeutic efficacy by overcoming the drawbacks of traditional inhalation therapies including low bioavailability rapid clearance and poor deposition. Various nanocarrier types—polymeric lipid-based liposomes and hybrid systems—as well as formulation and characterization techniques and physiological barriers that impact deposition and retention are covered. The future potential of pulmonary therapies enabled by nanotechnology is outlined by highlighting emerging developments such as aerodynamic optimization stimuli-responsive and targeted DPI systems safety regulatory and translational considerations.

DRUG SELECTION CRITERIA FOR DPI

1. Appropriateness for pulmonary administration (rapid systemic onset or therapeutic target in the lung).

2. Potency in accordance with microgram–milligram dosage[2]

3. Physical-chemical characteristics that allow for the production of aerodynamic particles between 1 and 5 μm.

4. Low hygroscopicity or the possibility of stabilization with excipients along with acceptable powder flow.[9]

5. Proven dissolution in lung fluid simulation or particle engineering readiness as well as expected inhalation safety and large-scale manufacturing. As per the Quality Considerations Guidance for Industry regulatory guidance for inhalation products analytical procedures and stability studies were planned.[10]

COMPOSITION OF CARRIER USED IN DPI

Despite being pharmacologically inert excipients are essential for improving formulation performance. They lower particle adhesion enhance powder dispersion and enhance the active pharmaceutical ingredients (API) mechanical strength chemical and physical stability and release properties. Excipients improve taste and provide sensory feedback during inhalation help achieve the ideal particle size for pulmonary drug delivery and provide bulk for simpler handling and dosing. They also increase patient compliance.

1. Lactose: One of the main factors influencing drug release in dry powder formulations is the adhesion of the drug to the carrier particles. Lactose is the recommended option because of its safety profile but adding fine excipients is another tactic to control these interactions. Drug adhesion is decreased and dispersion is improved by fine lactose particles occupying high energy surface sites on the carrier through processes like multiplet formation triboelectric modifications and redistribution. These multiplets can either reach distal lung regions or aid in drug detachment. However too much fines incorporation can disrupt manufacturing processes like mixing and capsule filling and adversely impact powder flow.[11]

2. Mannitol: An alternative to lactose in inhalation powders has been investigated: mannitol a sugar alcohol. Since it doesn't reduce like lactose does it works well with APIs that contain amines. When mixed with excipients that increase the systems glass transition temperature or prevent crystallization mannitol despite having a low glass transition temperature can act as a stabilizer. The first authorized inhalable insulin formulation Exubera which included mannitol in addition to sodium citrate glycine and sodium phosphate served as an example of this.[12]**.** For dry powder inhaler (DPI) formulations, mannitol is becoming more and more acknowledged as a promising non-reducing, non-hygroscopic sugar alcohol that offers enhanced stability, patient compliance, and biologic compatibility. Nevertheless, its natural state frequently lacks the best surface and aerodynamic qualities, making particle engineering methods like surface modification, freeze drying, and recrystallization necessary. For instance, producing surface roughness on a nanoscale from saturated mannitol solutions improves the fine particle fraction and aerosolization effectiveness of medications such as salbutamol sulfate. To enhance drug detachment, engineered fine mannitol particles may also function as ternary additions with lactose. Further development of mannitol carriers with customized surface morphology and micromeritic characteristics may be able to get over lactose restrictions and expand the use of DPI in biologics and innovative treatments.[13]

3. Trehalose: A common stabilizing agent in spray-dried inhalation powders trehalose is a non-reducing glucose disaccharide with a high glass transition temperature (~106 °C) that forms a protective glassy matrix. Even though it makes biopharmaceuticals more stable while drying and storing its hygroscopic properties after spray drying can cause cohesiveness and recrystallization making handling and storage more difficult. Trehalose is frequently mixed with moisture-protective excipients like leucine to address this. Despite being widely accepted as safe in food the FDA has not yet approved trehalose as an excipient for inhalation.[12]

4. L-Leucine: L-Leucine, a nonpolar aliphatic amino acid, is the most extensively studied amino acid excipient in inhalation dry powders. Its inclusion in spray-dried formulations enhances aerosolization performance and mitigates the hygroscopicity of amorphous powders, which are otherwise prone to moisture-induced crystallization and agglomeration. Through its surface activity and low solubility, leucine forms a hydrophobic coating on particles, thereby improving their physical stability.[12]

5. Trileucine: Trileucine, a tripeptide composed of three leucine residues linked by peptide bonds, has been investigated as an excipient in inhalation dry powders. Similar to L-leucine, it improves aerosolization performance and enhances the physical stability of spray-dried formulations by reducing moisture sensitivity and particle aggregation. [12]

DIFFERENT NANOTECHNOLOGY APPROCHES USED IN DPI FORMULATIONS:

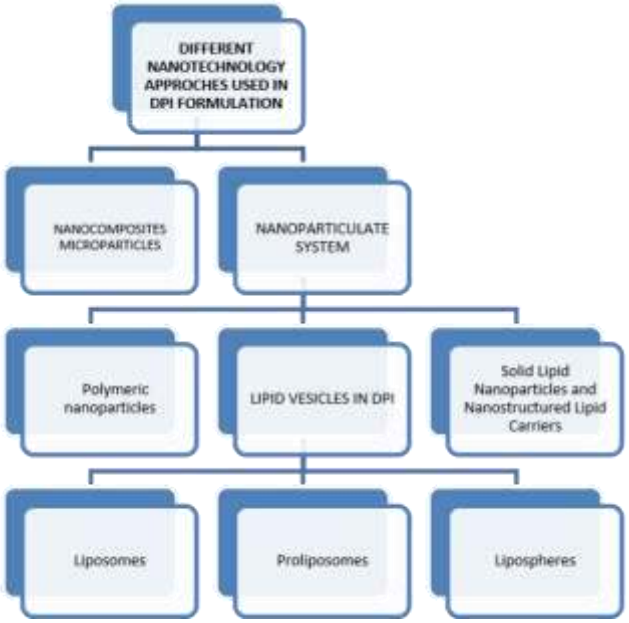

Fig. 1. Different Nanotechnology Approaches used in DPI Formulation

1. Nanocomposites Microparticles:

microparticle-based drug delivery systems are becoming more and more significant in respiratory therapy Because they can increase the therapeutic index prolong the drug half-life and lower toxicity. In order to allow for sustained release these micron-sized carriers encapsulate medications in films of natural or synthetic polymers with regulated thickness and permeability. Numerous varieties are appropriate for inhalation such as polymeric solid lipid large porous and drug–cyclodextrin complex microparticles. They are very effective for pulmonary delivery due to their deep lung deposition ability and resistance to aggregation. When used with dry powder inhalers they offer benefits like convenience ease of use and propellant-free operation.[14]

2. Nanoparticulate System:

a. Polymeric nanoparticles: The biocompatible and biodegradable polymers PLGA, PLA, chitosan, alginate and PCL are used to create polymeric nanoparticles (PNPs) which show promise as inhalation therapy carriers. Safety is ensured by the non-toxic by-products that these polymers break down into and surface modifications can improve targeting. PNPs are mostly taken up by cells through endocytosis which causes the therapeutics to be localized intra-lysosomally. Diffusion impaction sedimentation and interception are some of the processes that control pulmonary deposition and are all influenced by particle size. While diffusion is fueled by the Brownian motion of ultrafine particles interception happens when elongated particles follow airflow and make contact with airway walls. (Drugs Delivered by Nanoparticles in Inhaled Therapy: Enhancing Respiratory Health). For pulmonary arterial hypertension (PAH) treatment simvastatin nanoparticles greatly improve solubility and bioavailability when added to dry powder inhalers (DPIs). With a narrow distribution and a particle size reduction to about

100 nm (PDI = 0. 105) the solubility doubles from 0. 65 µg/mL to 1. 27 µg/mL reducing crystallinity during spray drying. This improvement avoids the extensive first-pass metabolism that limits oral bioavailability (~5 percent) and speeds up dissolution in lung fluid. In order to achieve effective lung deposition nanoparticles aggregate into respirable sizes (1–5 µm) (FPF = 20% MMAD = 1. 33 ± 0. 18 µm). When combined these characteristics allow for more effective treatment better pharmacokinetics and targeted pulmonary delivery.[15]

b. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: The first class of lipid nanocarriers are solid lipid nanoparticles (SLNs) which are made of biocompatible lipids that stay solid at room temperature and physiological conditions. They are usually 40–1000 nm in size. Low cytotoxicity sustained release with pseudo zero order kinetics drug protection and physicochemical stability are among the benefits of these formulations which contain 0–30 percent (w/w) lipid dispersed in aqueous surfactant solutions. The second generation of nanostructured lipid carriers (NLCs) are made up of partially crystallized lipid matrices that are created by combining solid lipids with oils in ratios ranging from 70:30 to 99. 9:0. 1 which results in a less ordered structure with a greater capacity for drug loading. Aerosolization of both SLNs and NLCs into respirable droplets allows for controlled release extended retention and effective lung deposition. SLN and NLC-based DPI formulations are promising for inhaled drug delivery because of their ability to increase patient compliance prolong dosing intervals and improve therapeutic outcomes.[16]

3. Lipid Vesicles In DPI

a. Liposomes: Comprising aqueous compartments surrounded by concentric lipid bilayers liposomes serve as slow-release reservoirs that extend drug exposure. When compared to free drug encapsulation decreases systemic absorption and encourages even distribution throughout the lung airspaces. This makes it possible to lower healthcare costs improve patient quality of life and reduce the frequency of dosing. The phase-out of propellants and the limited stability of aqueous liposomal dispersions underscore the potential of dry powder inhalers (DPIs) as the most practical substitute for administering liposomal formulations in dry form even though MDIs currently deliver a large number of inhaled medications.[17] To improve localized pulmonary delivery and offer extended drug retention for rescue therapy in transplant rejection a nano liposomal dry powder inhaler (DPI) of tacrolimus was created. The formulation demonstrated a high level of drug entrapment efficiency (96 percent ± 1 point 5 percent) prolonged in vivo lung residence for 24 hours and sustained in vitro release for up to 18 hours. When compared to plain tacrolimus lung exposure increased 1–8 times ($AUC_{0–24}h$) indicating enhanced bioavailability and long-lasting therapeutic effect. Additionally the optimized DPI showed outstanding aerosolization qualities allowing for effective deep lung deposition.[18]

As an alternative to traditional liposome powders proliposomes are phospholipid-coated carbohydrates that when hydrated in the pulmonary environment form liposomes. Techniques like spray drying, alcoholic phospholipid solutions or air jet milling phospholipid–drug blends with lactose can be used to prepare them. Multilamellar vesicles (MLVs) with entrapment efficiency and fine particle fraction (FPF) that depend on formulation are produced by these systems FPF values are usually between 20 and 30 percent. Powdered liposomes have great promise for inhaled antimicrobial

delivery and are appropriate for low-dose treatments like asthma. To ensure drug protection and efficient pulmonary targeting beclomethasone dipropionate (BDP) proliposomes for instance exhibit a high entrapment efficiency (94 percent).[19] [20]

b. Lipospheres: Lipospheres are self-contained spherical microparticles with a hydrophobic lipid core that is held in place by a phospholipid monolayer. They range in size from 0. 2 to 100 µm. Their solid lipid matrix improves physicochemical stability and bioavailability by allowing controlled drug release. DPPC/DPPG (75:25) was used to create a cyclosporine A (CsA) liposphere-based DPI through spray drying. With an FPF of 52. 99 ± 4. 12 percent an MMAD of 2. 79 ± 0. 47 µm and a GSD of 1. 85 ± 0. 05 aerosol characterization using a next-generation impactor showed good performance. In contrast to co-spray-dried CsA alone the lipospheres demonstrated enhanced aerosol dispersion reduced residual water content and superior physicochemical stability.[21]

Table no.1: Overview of Microparticle and Nanoparticle Drug Delivery Systems

Drug Delivery System	Characteristics	Active Pharmaceutical Ingredient	Method of Preparation	Size	Ref
Microparticles	Solid Lipid Microparticles (SLMs)	Quercetin	o/w emulsification method	5.72 µm	[22]
	Polymeric Microparticles (PLGA MPs)	Rifapentine	Spray drying	~2 µm	[23]
	PCL Microparticles (PCL MPs)	Resveratrol	Vibrational atomization spray drying	3.8 µm	[24]
Nanoparticles	Polymeric Nanoparticles	Heparin	Ionotropic gelation technique	162–217 nm	[25]
	Solid Lipid Nanoparticles (SLNs)	Budesonide	Emulsification–solvent diffusion method	218.2 nm	[26]
	Nanostructured Lipid Carrier (NLC)	Paclitaxel	Emulsification and ultrasonication method, spray drying	283.4 nm	[27]
	Liposomes	Curcumin	Nano-spray drying	2.10 µm	[19]
	Proliposomes	Synergistic Ciprofloxacin and Colistin	Ultrasonic spray-freeze drying	~100 µm	[28]

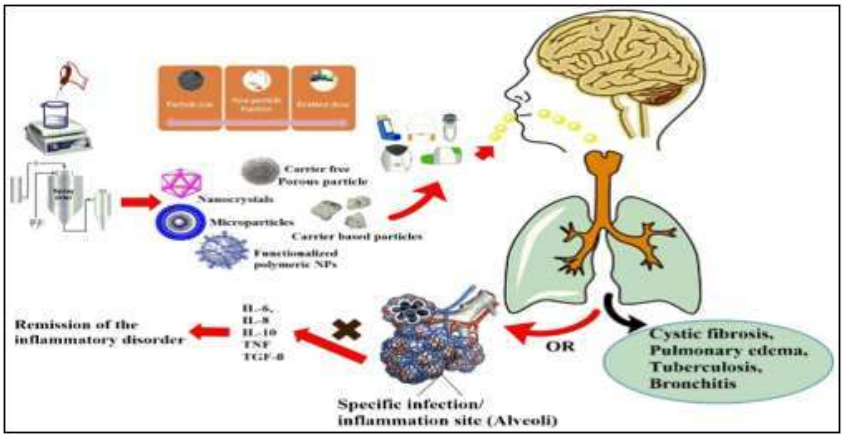

Fig. 2. Particle engineering for formulation of dry powder inhalation systems applicable in lung diseases[29]

MANUFACTURING OF DPI FORMULATION

By reducing coarse active pharmaceutical ingredients (APIs) and excipients to micron-sized dimensions usually from the submicron scale up to several tens of microns micronization is a particle engineering technique. Improved dissolution bioavailability of poorly soluble medications and the production of respirable particles for pulmonary delivery are all made possible by its ability to control particle size distribution morphology and surface area. Additionally micronization improves content uniformity and manufacturing reproducibility. A general classification of the techniques is bottom up (constructive particle formation e. g. A. antisolvent precipitation spray drying or top down (particle size reduction through impact shear or compression e. g. 3. milling homogenization under high pressure).[30]

a. **Spray Drying:** Developed as a particle engineering technique in the 1980s spray drying eliminates the need for coarse carriers and produces fine particles (2 μm) with desired flow and dispersion properties. It is a bottom-up method that minimizes thermal degradation from evaporative cooling by atomizing drug solutions into droplets that are quickly dried in a warm air stream. Both aqueous and non-aqueous systems can benefit from spray drying which makes it possible to create porous particles that are appropriate for pulmonary delivery. Process variables affect the properties of the powder (e. g. A. collection technique drying rate and nozzle type) and formulation parameters (e. g. G. drug properties). This method has been effectively used for sensitive APIs like proteins and peptides as demonstrated by enzyme formulations like superoxide dismutase and inhalable insulin (Exubera®). Additionally spray drying facilitates the pulmonary delivery of high doses (e. g. 3. antibiotics) and cutting-edge innovations like PulmoSphereTM. Moreover it makes it possible to create nanoparticle composites which makes it easier to deliver vaccines based on nanoparticles or poorly soluble drug nanocrystals to the nasal mucosa and lungs.[31]

b. **Spray freeze drying:** In spray freeze drying (SFD) a drug solution is atomized above a cryogenic liquid. The droplets immediately freeze and the solvent is then removed through lyophilization. Although this approach spares biomacromolecules from heat stress it presents problems like thermodynamic instability shear stress during atomization and protein adsorption at the air–liquid interface which can lead to aggregation. Therefore, stabilizing excipients are necessary to safeguard delicate biologics. In addition to being easier to handle during storage and transportation freeze-dried powders provide improved long-term stability by reducing degradation. Long processing times high energy consumption and expensive equipment however limit lyophilization. (An overview of dry powder inhaler production methods). For pulmonary delivery an optimized spray-dried formulation of beclomethasone dipropionate (BDP) with γ cyclodextrin was created by the study Optimization of spray-drying process variables for dry powder inhalation (DPI) formulations of corticosteroid/cyclodextrin inclusion complexes. Process variables were methodically assessed especially feed rate and inlet temperature. Under ideal circumstances (Tin 70°C feed rate 5 mL/min outlet 50°C) spherical particles (1–5 μm) with good

dispersibility and minimal residual moisture were produced. This formulation outperformed the commercially available Beclotaide Rotacaps achieving a respirable fraction of approximately 38% and emitting a dose efficiency of approximately 51% when combined with lactose (7:93). The results demonstrate that spray drying is a reliable technique for corticosteroid DPI development confirming that lower feed rates and higher inlet temperatures enhance particle uniformity and lung deposition.[32]

c. **Supercritical Fluid Particle Design (SCF PD):** Because supercritical fluid (SCF) technology is nontoxic inert cost-effective and environmentally benign it has garnered a lot of interest. When a substance is kept above its critical temperature and pressure it displays characteristics of both a liquid (high density strong solvating power) and a gas (low viscosity high diffusivity) making it supercritical. Temperature and pressure can be used to modify these characteristics increasing pressure improves density without appreciably altering viscosity. Numerous compounds have been studied as SCFs but the most common one in pharmaceuticals is carbon dioxide (CO_2). The Food and Drug Administration has recognized CO_2 as safe inert colorless odorless nonflammable economical and recyclable. Its critical temperature is 31°C and its critical pressure is 74°R.[33]

d. **Quality by Design (QbD) and Optimization / Factorial Designs approach:** A methodical risk-based and scientific framework known as Quality by Design (QbD) places a strong emphasis on careful initial design in order to guarantee constant product quality. Formulation and device design must be developed concurrently for dry powder inhalers (DPIs) which are categorized as combined products. The characteristics of the drug substance (particle size distribution morphology and crystallinity) susceptibility to temperature and moisture and excipient specifications (e. g. G. lactose) as well as device/packaging design to guarantee consistent dosage and delivery of fine particles. Through particle engineering sophisticated quality control techniques fixed dose combination inhalers innovative excipient carriers proliposome inhaler quality management and machine learning-assisted process optimization recent research has applied QbD principles to the development of DPIs. The development of cutting-edge DPI technologies is supported and quality assurance is improved by these strategies taken together.[34]**.** A carrier-free dry powder inhaler (DPI) was developed using the Quality by Design (QbD) framework in the study "A Drug–Drug Cocrystal of Favipiravir and Theophylline". The effects of solute concentration feed pump rate and atomizing air flow on important quality attributes such as MMAD FPF and crystallinity were methodically assessed using a three factor two level full factorial design. With an MMAD of about 2. 9 µm and an FPF of about 79 percent the optimized formulation showed good aerosolization and was appropriate for deep lung deposition. In order to support the logical design of drug–drug cocrystal formulations with enhanced pulmonary delivery and therapeutic efficacy the study verified that QbD facilitates a reliable repeatable process for DPI development.[35]

e. **Carrier-based Particles:** To improve the homogeneity dispersibility and therapeutic effectiveness of inhaled powders carrier-free

particles have been created. Spheroids of micronized budesonide (Pulmicort®) and porous PulmoSpheres® which are utilized in the Tobi Podhaler® (tobramycin) are two examples that are marketed. A new class of carrier-free particles has recently surfaced these particles are usually created by spray drying and have a solid core with an outer layer. Because of their small size (2–10 μm) and rough wrinkled surfaces these particles enhance deep lung deposition and aerosolization.[36] In order to overcome the drawbacks of carrier-free systems dry powder inhalers (DPIs) employ carrier particles in addition to the medication. The carriers three main purposes are (1) improving powder flowability to make it easier to fill capsules or devices (2) encouraging effective drug particle dispersion during aerosolization and (3) diluting the drug to allow for precise and repeatable dose administration.[37]

f. **Surface engineering / force control agents / surface energetics:** The excess energy at the particle surface relative to the bulk is known as surface energy which is an inherent characteristic of solid particles. Dispersive surface energy which results from van der Waals interactions caused by transient dipoles and polar surface energy which results from permanent dipoles or polar groups make up its two constituent parts. Intermolecular attraction and surface area are directly correlated with surface energy higher surface energy is produced by stronger attractions and larger surface areas. Surface energy affects the interparticle bonding between drug and carrier particles in dry powder inhaler (DPI) formulations. Lower surface energy produces weaker less stable mixtures whereas higher surface energy produces stronger adhesion and less detachment. Therefore surface energy measurement is an essential tool in formulation development and offers predictive insight into DPI performance.[38]

g. **CFD:** Both laminar and turbulent airflow can be simulated by computational fluid dynamics (CFD) models which can then be combined with particle dynamics models including the discrete phase model (DPM) two fluid model mixture model dense dispersed phase model and discrete element method (DEM) to forecast particle interactions and aerosol flow. Critical information about the performance of dry powder inhalers (DPIs) is provided by CFD. This information includes particle trajectories inhalation flow profiles and detachment behavior under flow stresses and wall impacts. Prior DPI research applications of CFD have mostly examined airflow patterns and particle motion in inhaler devices.[39]

h. **Invitro Testing In Cascade Impactors:** The cascade impaction (CI) method is a complex but widely used technique for characterizing dry powder inhalers (DPIs), as it allows direct assay of active pharmaceutical ingredient (API) mass in each fraction. By interpreting results in terms of aerodynamic particle diameter, CI accounts for both particle density and shape, providing a scale predictive of deposition in the respiratory tract. Particle motion in the respirable range (0.5–10 μm) is primarily governed by inertia, with sedimentation and diffusion playing lesser roles. CI-derived aerodynamic particle size distribution (APSD) data are therefore valuable for predicting lung deposition and potential clinical response. Inertial impactors, the basis of CI, separate particles by subjecting them to directional changes in airflow under laminar conditions, with

particles collected on plates containing jets of defined size.[40]

MECHANISM OF ACTION OF DPI

Inhalers that use dry powder are highly advanced machines. The user must inhale through the device for the active medication to reach the respiratory tract. Through a process known as deagglomeration, the energy from this inhalation breaks up the compacted drug powder and moves the de-agglomerated drug into the lung. The majority of DPIs contain a drug that has been micronized and combined with lactose or other carrier particles to provide adequate flowability and inhibit aggregation. Fine lactose particles are frequently added to the carrier lactose to saturate high-energy binding sites and easily detachable aggregates with the drug particles, thereby improving the aerosolization of the drug particles.[41]

The therapeutic ratio is higher with the pulmonary route than with the oral and parenteral routes because it enables the delivery of a relatively small amount of the active ingredient directly through the respiratory system, reaching a high local concentration in the airways while also reducing systemic side effects. Additionally, the lungs have highly effective clearance systems that prevent harmful environmental particles from entering the body. Drug deposition in the respiratory system is a crucial factor to take into account when evaluating the effectiveness of an inhaled dosage form. The first step following a successful particle inhalation is drug deposition, which can occur via a variety of mechanisms, including direct interception, electrostatic deposition, and inertial impaction, sedimentation, and diffusion (Table).[42]

Table 2. Deposition mechanisms in the lungs according to particle size.

Sr. No.	Particle Size	Mechanism	Parts of Respiratory Tract
1	Above 5 µm	Inertial impaction	Oropharynx and conducting airways
2	0.5–5 µm	Sedimentation	Bronchi, Bronchioles and Alveoli
3	0.5–3 µm	Sedimentation and Diffusion	–
4	Below 0.5 µm	Diffusion and Brownian motion	Alveolar region

The deposition of therapeutic aerosol particles onto the epithelial surfaces of the respiratory tract is governed by three predominant mechanisms: Brownian diffusion, which serves as the principal mechanism for particles measuring less than 0.5 µm; gravitational sedimentation, which is relevant for particles exceeding 0.5 µm; and impaction, which predominantly influences particles larger than 5 µm. Additional mechanisms that play a comparatively minor role in particle deposition encompass interception and electrostatic interactions that occur between the particles and the pulmonary walls.[6]

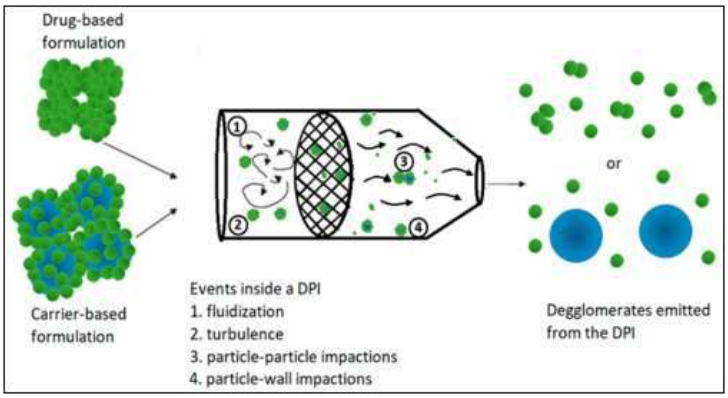

Fig. 3: Schematics-of-dry-powder-inhaler-DPI-dispersion-mechanisms Flow and Particle Modelling of Dry Powder Inhalers: Methodologies.[43]

a. Diffusion: Brownian motion or diffusional deposition is especially important for very small particles (submicron size) that build up in the alveoli and minor airways. The pulmonary dosage is optimized and the fraction of particles that are successfully delivered to their designated site is increased thanks to the careful engineering of advanced inhalation apparatus that releases tiny particles (1–5 μm in aerodynamic diameter). The rate at which aerosol particles are released from an apparatus and move through the airways as well as the inhalation flow rate can significantly impact the patterns of pulmonary deposition. A lower inhalation velocity tends to promote more peripheral deposition patterns whereas a higher inhalation velocity generally corresponds with increased deposition in the central and oro-pharyngeal regions. A slow inhalation flow however might not be sufficient to break up the powdered drug when using a low-resistance dry-powder inhaler which would limit lung deposition. In conclusion the most effective strategy for overall lung deposition and penetration into distal airways has been proven to date to be an inhalation device design paradigm that combines slow-moving aerosols with smaller drug particles or droplets.[20] According to the general form (Dtr)1/2 the deposition by diffusion is proportional to the diffusion coefficient D and the residence time tr. D is the particles diffusion coefficient. given by. where dp is the particle diameter g is the dynamic viscosity Cc is the slip correction factor T is the absolute temperature and k is Boltzmanns constant. This upper limit of the diffusion-dominated regime is the size at which the combined effects of impaction and sedimentation equal the effect of diffusion on DF. The comparison of the size-dependent DF curve (obtained from e. g. G. the ICRP model) between a hypothetical particle with zero density (DF due to diffusion only) and a spherical particle with a given density (DF due to diffusion impaction and sedimentation). The size of interest is the one for which the actual density (DF) is twice that of the zero density (DF)**.**[44]

b. Sedimentation: Sedimentation happens due to gravity, mainly seen in the narrow airways and alveolar spaces because of the short distance particles travel before hitting the walls. Particles sized between 1–5 mm are primarily set down through a sedimentation process. Particle deposition through sedimentation correlates positively with particle diameter or size and rises as airspace dimensions diminish. Consequently, sedimentation leads to greater particle deposition in the alveoli compared to the bronchi.[6]

c. Impaction: It impacts large particles, which possess significant mass and tend to move quickly. Large particles do not modify their flow path at the

narrow bifurcations, leading to a higher occurrence of this phenomenon as aerodynamic particle size increases.

d. Enzymatic Degradation: Degradative enzymes are present in the lungs, although far less frequently than in the GIT. The drug component in various delivery systems may be hydrolyzed by various enzymes based on its characteristics. Proteases, peptidases, and lipases are all included. CYP450 enzymes are also present and play a crucial role in metabolizing most medications.[45]

e. Electrostatic Charge Attraction: The electrostatic characteristics of particles lead to (a) both attraction and repulsion among particles from space charge forces, impacting agglomeration and interactions with other particles; and (b) attraction between particles and neutral inner airway surfaces due to image charge forces. At high particle number density, space charge force deposition prevails, while image charge the it force deposition becomes significant for lower density particles.[46]

CHARACTERIZATION AND EVALUATION OF DRY POWDER

Dry powder formulations call for a specific technical design and manufacture. The formulation should be processed in a way which makes the discharge of the device formulation-containing compartments and the duplicability of the dose measured undemanding. The formulation should also be satisfactory and suitable so that the API reaches and deposits on the desired target area with an appropriate flow rate. As a result, the drug and carriers should be present in an adequate aerodynamic size distribution, and then be dispersed properly in the airstream inhaled by the patient.[47][42]

a. **Aerodynamic Particle Size Distribution Of Dpi Products:** The APSD of DPI batches was examined as a key quality attribute.[48] The performance of dry powder inhalers (DPI) is measured by fine particle fraction (FPF) and emitted dose (ED), which are influenced by particle mass median aerodynamic diameter (MMAD). Optimal lung deposition is achieved with particles of MMAD between 1 to 5 μm. Past study noted that the static, bulk, and solid state properties of lactose in DPI enhance aerodynamic behavior and respiratory deposition.[49] Recently, the next generation impactor (NGI) has been employed to preparatively isolate powder fractions by aerodynamic particle size through dispersion and recovery of material. A constant flow rate in the NGI allows for the calculation of deposit aerodynamic particle size. The impactor's operation remains unaffected by the powder's physicochemical properties, enabling attribution of aerosol performance differences to particle physicochemical characteristics rather than aerodynamic size.[50]

b. **Particle Shape:** The impact of particle morphology on aerosolization efficiency has been extensively studied. It explored carriers with various morphologies to study the impact of elongation ratio (ER). They determined that an increased ER results in a higher delivery of salbutamol sulfate to the lung's lower airway areas, suggesting improved DPI efficacy.[37] The results of this research indicated that pollen- and spherical-shaped aerosol particles exhibit a greater FPF compared to the other particle shapes examined in this study. Pollen-like particles possess a porous surface structure and exhibit a lower density than those shaped like spheres, cubes, and plates. Aerosol particles with uneven surfaces lack

close proximity to one another, which diminishes their cohesive force for dispersion. Earlier studies discovered that particles with wrinkled surfaces dispersed more than those with smooth surfaces.[51]

c. **Electrostatic Charge:** The size of the particles and their surface shape also influence the electrostatic charges present on the particle surface. Minor aerosol particles possess more uniform shapes and surfaces compared to larger particles. Decreasing the aerosol particle size boosts the electrostatic surface charge of the particles, which reduces the FPF and enhances the cohesiveness both among the particles and between the DPI surface wall and the particles.[51]

d. **Entrapment Efficiency:** The drug levels were assessed from the microparticles or nanoparticles. The drug was isolated from microparticles using various solvents. After suitable dilutions, the drug content was measured in a UV/V is spectrophotometer. Entrapment efficacy was calculated using the following formula:

Entrapment efficacy = (estimated % drug content) / (% drug content theoretical) × 100. [6][52]

In the domain of pharmaceutical manufacturing, the primary objective is to attain an encapsulation efficiency (EE) approaching 100% in order to effectively integrate the active pharmaceutical ingredient into the carrier system while minimizing material loss. No significant discrepancies in the reported EE of the two predominant production methodologies were observed. A substantial proportion of the investigations employed the technique of hot homogenization. Nevertheless, thermal treatment has the potential to degrade the drug intended for incorporation. This complicates the assessment of the impact of thermal application on the drug, relegating the analysis to theoretical considerations informed by alternative data and molecular architecture, thereby underscoring the necessity for drug recovery evaluations as outlined in the subsequent section.[53]

e. **Percentage yield[54]:** The practical yield was determined through direct measurement of the powder produced by the dryer units The percentage yield of each formulated batch was calculated by utilizing the following expression:

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

f. **In Vitro Drug Release Study:** The in vitro drug release evaluation of the DPI formulation was conducted using modified USP dissolution apparatus type I equipped with a dialysis membrane. This dialysis membrane facilitates the separation of drug molecules that have been released, enabling their free passage into the dissolution medium. The dissolution process was carried out in PBS buffer at pH 7.4 (100 mL volume) maintained at 37.5°C. Samples for dissolution analysis were collected at hourly intervals for a duration of 8 hours, properly diluted, and the amount of drug released into the medium was analyzed using a UV spectrophotometer (Shimadzu, UV-1800, Kyoto, Japan) at a wavelength of 256 nm. During each sampling time point, equivalent volumes of fresh medium were added back to preserve sink conditions. To determine the mechanism governing drug release from these formulations, various kinetic models were

employed, including zero order, first order, Higuchi matrix, and Korsmeyer-Peppas models (PCP Disso V3, India). The coefficient of correlation values and release rate constants were determined to verify model appropriateness, which simplified the sampling process and prevented unnecessary sample loss during preparation and manipulation procedures. The dialysis membrane used in this study had a molecular weight cutoff ranging from 12,000 to 14,000 Dalton.[55]

g. **In Vivo Studies:** Live animal experiments are conducted to assess pulmonary absorption and the distribution patterns within the lungs. To achieve this objective, the pharmacokinetic characteristics and distribution across various lung regions are examined using multiple animal species, such as rats and guinea pigs. Dosing techniques including intratracheal administration, micro-spraying, nebulization, and aerosol delivery are employed to introduce NLDPFs into the animals. Drug concentrations in tissue homogenates from different lung lobes and bronchoalveolar lavage fluid are measured at specified time points to determine both the quantity of drug deposited and the distribution characteristics throughout the lungs. The drug levels in blood samples and tissue homogenates from other primary organs are analyzed to evaluate systemic uptake following inhalation of DPFs. Our laboratory has established validated analytical procedures to determine the pharmacokinetic profiles of medications in rat models.[56]

h. **Electron Microscopy:** The surface structure and morphology of the synthesized microparticles were examined using scanning electron microscopy (VEGA3 LMU, TESCAN) capable of achieving magnifications up to 1,000,000X and a resolution of 3 nm at a peak voltage of 30 kV. Digital recording of electron images was performed at elevated magnification levels. The scanning electron microscopy technique enabled visualization of particle size, structural characteristics, and surface features of the DPI microparticles. Powder samples were mounted on adhesive-coated aluminum stubs with a 6.25 mm radius. Excess powder was eliminated by gently tapping the stub and applying a stream of particle-free compressed air. Subsequently, the samples were analyzed using scanning electron microscopy operating under maximum vacuum conditions with an acceleration voltage ranging from 5 to 15 kV and maintaining a specimen working distance of 12 mm.[52]

i. **Scanning DSC Studies:** Powder or additives were enclosed within the flat-bottomed aluminum container of the differential scanning calorimeter (DSC TA-60WS, Shimadzu, Japan). An empty reference pan was placed alongside each sample pan to compensate for the thermal effects of pure aluminum. Both the sample and reference were subjected to continuous nitrogen gas purging at 25 mL/min flow rate. Data acquisition occurred across a temperature span from 20 to 320°C with a heating rate of 10°C per minute. Melting point and phase transition determinations were conducted using the instrument's accompanying software.

j. **Solid State Characterization Of Dry Powder**[57]**:** A powder pile was carefully formed through a funnel that was placed 2 cm above the surface in order to calculate the angle of repose (θ). The following formula

was used to determine the angle. H/r = tan θ. where r is the piles radius and h is its height. Additionally measured were bulk density (BD) and tapped density (TD). A 10 mL graduated cylinder was filled with 2 g of API powder for this purpose and the initial volume was noted. After that the cylinder was free to drop from a height of 2 to 5 cm at 2-second intervals until there was no more noticeable change in volume. Utilizing the following formulas BD and TD were determined.

BD = Powder blend weight divided by packings untapped volume.

TD = Powder blend weight divided by packings taped volume.

By applying the following formula to calculate Carrs Compressibility Index (CI) the flowability of the powder blend was further evaluated.

$$CI = [(TD-BD) \times 100] / TD$$

k. **Fourier-Transform Infrared Spectroscopy:** Using an FT-IR spectrometer (Thermo NicoletAVATAR 330; LabX Midland, ON, Canada), Fourier-transform infrared spectroscopy (FT-IR) spectra were recorded at an optical resolution of 4 cm-1 between 4,000 and 400 cm-1. In an agate mortar, the sample was combined with 150 mg of dry KBr, and the mixture was compressed to create disks that could support themselves at a weight of 10 tons.

l. **X-ray powder diffraction:** An X-ray powder diffraction (XRPD) BRUKER D8 Advance X-ray diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) was used to characterize the crystal structure of spray-dried powders in combination with various excipients. A Cu Ni radiation source with a slit detector was used to measure the powder samples after they were loaded onto a plane quartz glass sample slide with an etched square. The following settings were made: angular step 0.010°, time constant 0.1 s, voltage 40 kV, and current 40 mA.[58]

Since the processes involved are rather complex, thorough testing is necessary to ensure the efficiency, quality, and safety of the formulation through general and supplementary tests are as follows in this table:[59][60][61]

Table no. 3: Analytical and Quality Evaluation Parameters for Dry Powder Inhalers (DPIs)

Sr. no.	Test	Description
1.	Particle size determination	The determination is carried out either by light scattering decay or by a cascade impactor. µm is used to express the particle size.
2.	Fine Particle Fraction (FPF)	determines the percentage of fine particles typically. which are released from the DPI below 5 µm. demonstrating their appropriateness for deposition in the deep lung.
3.	InVitro Aerodynamic Assessment	Analyzes the emitted materials aerodynamic behavior and particles with the Mass Median Aerodynamic Diameter (MMAD) as one example.
4.	Content uniformity	Evaluates how evenly distributed the active is. pharmaceutical component (API) in the formulation of the DPI.
5.	Dose uniformity	Amount of actuation weighs the dose to ensure uniformity both before and after a particular event. The weight variation per dose is computed.
6.	Delivered dose	The dose is given for each actuation satisfies regulatory standards and corresponds to the recommended dosage.
7.	Moisture content	Uses techniques like gas chromatography or Karl-Fischer to measure the moisture content.

8.	Tapped density	Evaluates by measuring the tapped density. The packing capacity of the powder.
9.	Bulk density	Calculates the DPIs bulk density and formulation through the use of techniques such as pycnometry.
10.	Flowability	Assesses the DPIs flow characteristics. Formulation which may have an impact on device metering and the spread of aerosols.

MARKETED FORMULATION OF DPI

Table no. 4: Dry Powder Inhaler (DPI) Products and Their Characteristics[62][63]

Brand (device)	Active ingredients	Device type (DPI)	Main indication	Manufacturer
ADVAIR® Diskus / Seretide Accuhaler	Fluticasone propionate + Salmeterol	Diskus / Accuhaler (multidose blister DPI)	Asthma, COPD (maintenance)	GlaxoSmithKline (GSK)
SYMBICORT® Turbuhaler	Budesonide + Formoterol	Turbuhaler (multi-dose DPI)	Asthma, COPD (maintenance)	AstraZeneca
PULMICORT® Turbuhaler	Budesonide	Turbuhaler (multi-dose DPI)	Asthma (maintenance)	AstraZeneca
ASMANEX® Twisthaler	Mometasone furoate	Twisthaler (cap-activated multidose DPI	Asthma (maintenance)	Merck / Organon (region dependent)
SPIRIVA® HandiHaler	Tiotropium bromide	HandiHaler (capsule DPI)	COPD (maintenance)	Boehringer Ingelheim
ULTIBRO® Breezhaler	Indacaterol + Glycopyrronium (dual bronchodilator)	Breezhaler (capsule DPI)	COPD (maintenance)	Novartis
BREO® ELLIPTA	Fluticasone furoate + Vilanterol	Ellipta (pre-metered multi-dose DPI)	Asthma (maintenance), COPD (maintenance)	GSK (in some markets with partners)
ANORO® ELLIPTA	Umeclidinium + Vilanterol	Ellipta (pre-metered multi-dose DPI)	COPD (maintenance)	GSK / Partners

RECENT ADVANCEMENT AND FUTURE PROSPECTIVE OF DPI

Recently, innovative characterization methods that integrate optical photothermal infrared (OPTIR) spectroscopy with atomic force microscopy infrared (AFM-IR) spectroscopy have emerged to clarify the distribution of excipient and drug particles at submicrometer and nanometer levels.

Spray freeze drying (SFD) is an established method for producing large porous particles (LPP) in the realm of inhaled medications. It possesses a rapid production rate and is ideal for heat-sensitive substances. The entire procedure comprises three parts: atomization, freezing, and lyophilization. Recently, aerogels, which can be produced using SCF technology, have been investigated for their application in the development of porous particle formulations because of their varied textural properties and porosity.

Alongside the progress in DPI formulation design, developments are ongoing in device technology with the launch of innovative designs and digital advancements. The incorporation of digital technology allows these digital DPI platforms to offer extra insights into inhaler performance and/or usage, potentially reducing device use mistakes. This has demonstrated a beneficial effect

on product usage and effectiveness, along with patient satisfaction, compliance, and adherence, leading to improved clinical outcomes overall.

The digital DPIs that are currently approved by the FDA consist of the Digihaler® utilized with ProAir®, AirDuo®, and Armonair® products, which received approval in 2018, 2019, and 2020, respectively. The Digihaler® features a built-in digital sensor located within an electronic module (eModule) at the upper part of the inhaler, capable of tracking usage (date and time), inhalation data pertaining to the inhalation technique (e.g., PIF and flow volume), and offering medication reminders. The accuracy, advantages, and results of digital DPIs like the Digihaler® are starting to become evident. Additional FDA-approved digital DPIs featured external sensors instead of being completely incorporated into the device. The Propeller® sensors created for various DPI devices such as Diskus® (GlaxoSmithKline, Brentford, UK), Ellipta (GlaxoSmithKline, Brentford, UK), and Neohaler (Novartis, Basel, Switzerland) received FDA approval via the 510(k) pathway in 2015, 2016, and 2018, correspondingly. The Propeller® sensors technology captures and tracks actuation events (date and time) and employs Global Positioning System (GPS) technology to detect environmental triggers for asthma exacerbations. Moreover, the Hailie® sensor (cleared through the 510(k) process) was created for MDIs along with the Diskus® (SmartDisk™) and HandiHaler® (SmartHandy™), which can be affixed to the inhaler to monitor and log medication usage and establish reminders. Finally, the launch of the Staccato inhalation platform showcases ongoing advancements in device design for inhalation powders.[64]

Dry powder inhalers (DPIs) hold significant future potential for treating systemic disorders, with ongoing research focusing on novel and smart pulmonary drug delivery formulations, including microparticle and nanoparticle systems These advanced formulations aim for sustained and extended release, improved retention in the lungs, and active targeting Device design is also evolving, with DPIs becoming simpler and easier to use, and energy-powered active DPIs gaining popularity to overcome dependence on patient inspiratory flow Digital inhalers, equipped with features like reminders, alerts, and data collection, are emerging to enhance patient compliance and therapeutic benefits Furthermore, DPI applications are expanding to include vaccines and antiviral drugs, showing great promise for combating pandemics like COVID-19 through pulmonary vaccinations. In summary, despite past challenges and ongoing issues like limited excipient selection and variable lung deposition, the continuous advancements in formulations and device technology, particularly for systemic diseases and vaccines, indicate a promising future for DPIs.[65]

CONCLUSION

Dry powder inhalers have developed into strong platforms that offer systemic and targeted therapy via the pulmonary route while fusing scientific innovation with patient convenience. Modern manufacturing nanotechnology and engineered excipients have greatly enhanced drug stability deposition and therapeutic results. But there are still issues like patient inhalation variability limited excipient approval and the requirement for long-term safety data. To turn laboratory success into actual clinical impact and establish DPIs as a mainstay of upcoming respiratory and systemic therapies it will be essential to close these gaps through integrated formulation–device design and regulatory alignment.

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