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PHARMACEUTICAL CHARACTERISTICS OF DRY POWDER INHALER DESIGN: A COMPREHENSIVE REVIEW

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ABSTRACT

Asthma and Chronic Obstructive Pulmonary Disease (COPD) can be effectively treated with dry powder inhalers (DPIs), which are commonly used for pulmonary medication delivery. In order to optimize medicine formulation, particle engineering, and excipient selection, powder technology is essential. The powder's qualities, such as its size, shape, flowability, and surface features, are critical to the effectiveness of DPIs. Drug dispersion and deposition in the lungs are improved by designing carrier particles with regulated surface texture and aerodynamic characteristics. Improvements in powder processing methods like surface coating, spray drying, and micronization have increased the homogeneity of particles and the effectiveness of medication administration. Additionally, to improve dosage emission and consistency, the cohesive and adhesive forces between drug particles and carriers can be adjusted. Powder technology advancements also make it easier to create high-performance DPIs that can deliver biologics and small-molecule medications. Pharmaceutical scientists can improve patient compliance and treatment efficacy by concentrating on enhancing powder characteristics and device interactions. The significance of powder engineering in DPI design is emphasized in this review, along with how it contributes to better treatment results and efficient pulmonary drug delivery.

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Keywords: Dry Powder Inhalers (DPIs); Pulmonary Drug Delivery; Powder Technology; Particle Engineering; Drug Deposition.

1. Introduction

DPIs are inhalation devices used to treat respiratory conditions like pulmonary infections, asthma, and chronic obstructive pulmonary disease (COPD) by delivering powdered drugs to the respiratory tract. DPIs rely on patient inhalation to scatter and distribute the medication particles, as opposed to pressurized metered-dose inhalers (pMDIs), which need propellants. Particle size, flow characteristics, and drug stability must all be optimized for effective drug deposition in the lungs, which is a crucial pharmaceutical component.

The effect of irregular particle shape on dry powder inhaler (DPI) formulations was examined by Hickey et al. (1993). Their research described the characteristics of powders and looked at how they affected the functionality of medication delivery devices. Subsequently. examined the impact of morphological variations in drug particles of comparable size,

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highlighting the fact that shape variations have a major impact on the drug's aerosolization and distribution from DPIs.

Additionally, Zeng et al. (2000) investigated the effects of carrier particle surface properties on drug dispersion and deagglomeration. They emphasized that changes in medication distribution from batch to batch may result from morphological variances. According to their findings, the respirable fraction of salbutamol sulfate in dry powder formulations may be improved by altering carrier particles to take on particular forms, such as increasing surface smoothness or elongation.

In order to optimize lung deposition for both targeted and systemic drug administration, Musante et al. (2002) investigated important aerosol parameters, specifically particle density and size distribution. Crowder et al. (2002) used Stokes' equation to forecast how drug particles would aerosolize, highlighting the need of comprehending the connection between particle shape and aerodynamic characteristics in order to maximize drug delivery effectiveness in DPIs. The crystallization process of salbutamol sulfate from aqueous solutions and designed lactose crystals with different elongation ratios was also examined by Larhrib et al. (2003). According to their research, using needle-shaped drug particles in place of micronized salbutamol sulfate improved deposition, especially when paired with needle-shaped lactose transporters.

The function of vibrational energy in powder dispersion was studied by T. Crowder et al. (2006), who showed that certain vibrational inputs could enhance dosage emission and repeatability. According to their research, DPI performance may be improved and consistent medication delivery could be ensured by modifying energy input based on the flow characteristics of a particular formulation. The performance of pollen-shaped hydroxyapatite (HA) carriers and traditional lactose (LA) carriers was evaluated by Hassan et al. (2010), who came to the conclusion that the special shape of pollen-shaped carriers permitted larger drug mixing ratios without sacrificing delivery efficiency. According to their research, these carriers improve drug release from DPI formulations and are especially useful at low inhalation flow rates.

According to Peng et al. (2016), surface roughness, carrier particle characteristics, and particle morphology are some of the crucial elements affecting DPI performance. Their results supported the hypothesis that improving these traits could result in more effective medication administration. Benke et al. (2017) investigated many surface modification methods, including recrystallization, fluidized-bed coating, and mechanical dry coating, and examined the variables influencing lung deposition in carrier-based DPI systems.

Their research demonstrated how pulmonary deposition and medication dispersibility might be improved by enhancing interparticle interactions. The aerodynamic behaviour of variously shaped drug microparticles was finally examined by Ali et al. (2019), who found that triangular-shaped particles with a 2:1 aspect ratio had better flowability and less drag force. According to their research, utilizing triangular-shaped medication particles instead of traditional spherical ones could greatly increase powder dispersibility and breathing efficiency.

Because of developments in powder formulation technology, dry powder inhalers (DPIs) are a mainstay of pulmonary medication delivery. Aerodynamic particle sizes between 1 and 5 m are maintained in modern DPI formulations to guarantee effective lung deposition. The market is dominated by carrier-based systems that use lactose carriers because they can guarantee dosage homogeneity and enhance powder flowability (Mehta et al., 2025, Xiroudaki et al., 2025). On the other hand, dispersion and dosage uniformity are frequently issues with carrier-free formulations made up of cohesive drug particles.

In order to improve drug-carrier interactions and increase respirable fractions, surface modification techniques such as fluidized-bed coating and mechanical dry coating are employed to solve these problems (Mehta et al., 2016). Additionally, advancements in biomaterials and nanotechnology allow for fine-grained control over particle density, surface properties, and morphology, which lowers variability and improves drug delivery effectiveness (Ye et al., 2022).

In order to reduce batch-to-batch variance, continuous manufacturing procedures are becoming more popular, but spray drying is still the method of choice for creating amorphous solid dispersions (Cheng et al., 2020). These developments in formulation technique are essential for respiratory treatments as well as the

new uses of DPIs in systemic drug delivery, such as the delivery of mRNA vaccines and biologics (Mohan et al., 2022). In the upcoming years, DPIs stand to gain more therapeutic accuracy and patient adherence with additional formulation engineering advancements.

Drug Formulation and Particle Engineering

DPI formulation entails creating medication particles that are effectively aerosolized and deposited in the lungs. Among the main factors to be taken into account are:

Particle Size and Aerodynamic Properties: Particles between 1 and 5 μm are optimal for pulmonary deposition. While tiny particles (<1 μm) may be exhaled without deposition, larger particles (>5 μm) have a tendency to deposit in the oropharynx.

Micronization Techniques: To obtain the required particle size distribution, jet milling and spray drying are often employed techniques. Better control over particle morphology, density, and dispersibility is possible with spray drying.

Surface Modification: Enhancing dispersion and decreasing particle aggregation can be achieved by engineering particle surfaces with excipients such as mannitol or leucine.

Table: 1 Different Properties and their Parameters (Tiwari at al., 2021).

Properties	Parameters
Characteristics of Aerosol	The geometric standard deviation (GSD), mass median aerodynamic diameter (MMAD), and fine particle fraction (FPF) Air or particle velocity
Characteristics of particles	The aerodynamic diameter The density of bulk Size, shape and charge
Characteristics of physiochemistry	The ability to dissolve
	Hygroscopic conditions

1.1 Various methods used for the preparation of the pharmaceutical aerosol:

Several approaches are known for the preparation of inhalation particles, including the value, Variability and adaptability, and other features of APIs and how they facilitate engineered particle technologies. A few preparation procedures are listed below.

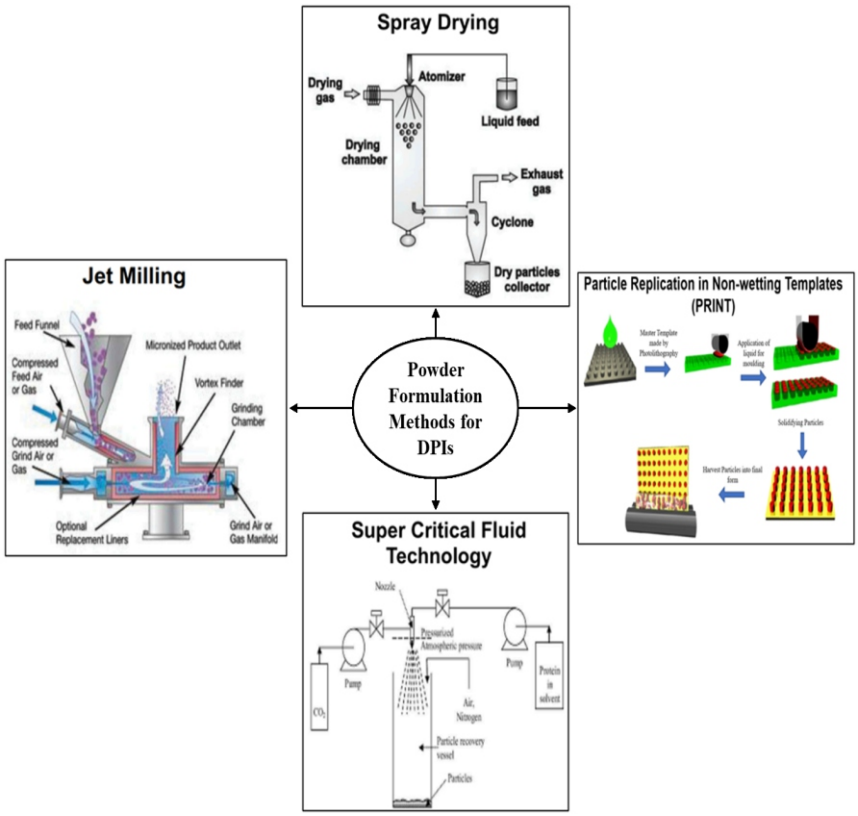

Fig. 1: Different Technologies for Powder Formulation. [Tiwari et. al.]

1.1.1 Milling:
Although the drop-down method offers the appropriate range of particle sizes, it is devoid of information regarding the particle breakage mechanism. Shah and associates (2017) Therefore milling does not always benefit from the logical modification of a particle's dimensions, density, or surface characteristics. However, milling can change the properties of the surface and the size of the particles [Luner et al., 2012]. It affected the hydrophobic and particle flow characteristics of the powder [Feeley et al. 1998, Heng et al. 2006].

The same is true for higher-dose powdered materials, which do not depend on the coarse additives to achieve their significant flowing capability. Luner et al. studied dry as well as wet grinding using succinic acid and sucrose and discovered that wet grinding had a slightly higher surface energy content due to its greater susceptibility to stress from mechanical contact.

1.1.2 Spray drying:
This is the grassroots strategy of producing customized particles. Spray drying was thoroughly reviewed by Vehring et al. The nozzle is used to spray the drug's solution, and the droplets are then dried in a heat chamber. This technique creates tiny particles by adjusting the size of the droplets.The literature also supports the presence of amorphous spray-dried particles and the drug's greater chemical stability compared to other forms (Chawla et al., 1994, Bosquillon et al., 2004). To maintain the stability of the medications in spray drying and storage conditions, excipients, such as sugar, might be dissolved within the drug. Using improved enhancers and drug release mechanisms for respiratory medication delivery can increase spray-dried particle performance.

Supercritical Fluid Technology:
This approach to producing micronized medication particles is quite modern. Most significantly, even at high temperatures, their morphological characteristics and APIs do not change; nonetheless, excessive pressure may have an impact on the drug aerosol's action. Even now, this method may not be an effective way to produce vaccines because it reflects viral inactivation (Winters et al., 1996 and Dillow et al., 1999).

1.1.3 Particle Replication in Non-Wetting Templates Technology:
Based on their size, shape, and flowability, this technique is now routinely employed to create effective medication particles. In particle engineering technology, this is also known as PRINT [Gratton et al., 2008] and is employed for the "micro melding" of particles. The active pharmaceutical ingredient (API) or API is pressed with an excipient in a micro-mold to create distinct particle sizes and shapes. With a mean median aerodynamic diameter (MMAD) of 3 m, the particle produced by this technique is appropriate for respiratory administration (Mack et al., 2012).

1.2 Factors affecting the aerosol performance:
Materials or fluids suspended in a gaseous medium is necessary for the formation of aerosols (Bosquillon et al., 2004). The treatment affects the solid nanoparticles. Method, but the liquid droplets have a circular shape (Garcia-Contreras et al., 2007). When particles become stuck in a flow, it is expected that the gas (air) will follow its path. Low circulation and fast flow speed are characteristics of the laminar flow regime.

These are the results of particle forces including thermal, gravitational, and electrostatic inertia, which cause the particles' route to diverge from the streamline (Crowder et al., 2002).

1.2.1 Aerodynamic nature of pharmaceutical aerosol:
The accumulation of drug molecules in the lungs of humans is largely determined by the aerodynamic behavior of pharmaceutical aerosols. Dimensions, shape, the density, and air resistance of particulate are some of the variables that affect aerosol dynamics. Taking into account the particle's size and density, the aerodynamic diameter is frequently used to forecast particle deposition. The idea of an analogous spherical particle with unit density (1 g/cm^3) is used to define it. In general, particles having aerodynamic sizes between 1 and 5 μm are most suited to enter the lower respiratory tract (Tajber et al., 2009).

1.2.2 Slip:
When the particle size is tiny in relation to the mean free path of air molecules, a divergence from Stokes' law known as "slip" occurs (usually in submicron particles). The slip correction factor (C) is used to quantify slip in pharmaceutical aerosols in order to account for non-continuum effects.

Drag force is less than what Stokes' rule predicts because the factor rises as particle size falls. For nanoparticles or small aerosol particles (less than 1 μm), slip correction becomes important.

1.2.3 Particle Density:

An essential physical criterion for determining a particle's aerodynamic diameter is its density. The sphere with the same density as the particle has the same settling velocity and the same aerodynamic diameter [49]. where, can be shown as follows:

$$d_{ae} = \sqrt{\rho_p}\, d_g$$

where is the particle's geometrical dimension and density. To enhance the effectiveness of medication particle transport into the respiratory system, a large geometric diameter and low density are required. The deposition into the upper and lower portions of the respiratory system is depicted in this graph.

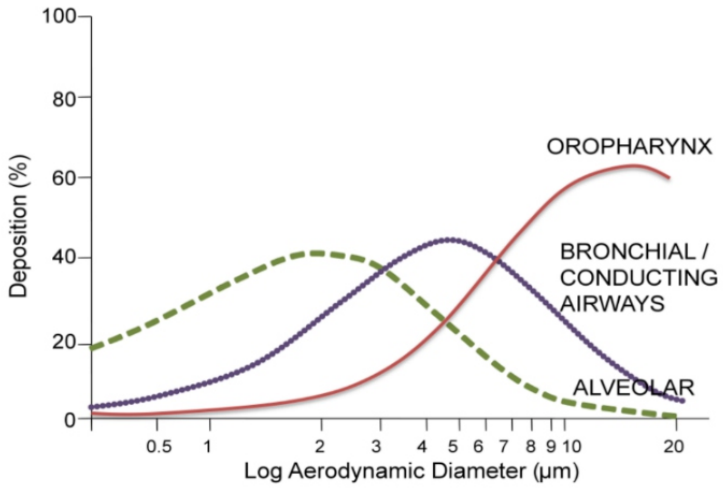

Fig: 1 This graph represents the relationship between drug deposition into lung and aerodynamic diameter (d_{ae}) (Köbrich et al., 1994).

1.1.1 Hygroscopic Properties of particle:

The amount of moisture in hygroscopic aerosols varies according to a certain temperature and relative humidity level. According to Zijlstra et al. (2004), Najafabadi et al. (2004), and Learoyd et al. (2008), it is significantly more important for the aggregation and dispersion of drug particles as well as for mobility of particles into airways and their aerodynamic characteristics. Pharmacological aerosols frequently experience hygroscopic buildup (Gilani et al., 2004).

1.2 Aerosol Agglomeration and deagglomeration process:

When the formulation of dry powder The same forces that attract molecules also affect particles. They are classified as mechanically interconnected, capillary force, electric force, and Van der Waals force.

1.2.1 Vander Waal force:

These result from the medicinal particles' contact impact. According to David et al. (2008), the particle is thought to be hard and homogeneous, and it describes the origin adhesive/cohesive forces that are proportionate to their particle size.

For the two similar particles $R_1 = R_2 = R$

$$F_{VdW} = \frac{AR}{6h^2}\frac{R_1 R_2}{R_1 + R_2} = \frac{AR}{6h^2}$$

For particle and surface R2>>>>R1

$$F_{VdW} = \frac{AR}{6h^2}$$

Where A, R & h are representing the Hamaker Constant ($A \sim 10^{-19}$ J), Particle radius(m) & Separation Distance.

The geometrical and dimensional characteristics, such as particle morphology, size, and roughness, determine the Vander walls force considerably more. The precise assessment of the Vander walls force between the pharmaceutical particles is impossible due to their heterogeneous and malleable character, which makes it challenging to determine the precise value of the Hamaker constant.

1.1.1 Capillary force:

Three processes—adsorption, capillary condensation, and deliquescence—allow water to interact with solid particles, depending on the characteristics of the

particles and the relative humidity (Gavini et al., 2006). By increasing the particle contact force, a higher relative humidity value reduces the aerosol's dispersion ability. Cook et al. (2005) provide the following representation of the capillary force:

$$F_{cap} = 4\pi R^{*} y_L \cos\theta + 4\pi R^{*} y_{SL}$$

They are represented by the water surface tension, contact angle, hormonic mean particle radius, and interface tension between solid and liquid. y R*, θ, yL, and YSL.

1.1.1 Electrostatic force:

The electrostatic forces are less than the Vander Waals forces and have an attracting and repulsive nature for medicinal particles. The conductivity of the drug particles is low. It is necessary to take electrostatic forces into account. According to Rabani and Seville (2005), it was produced by tri boelectrification, coulombic interaction, and contact charging. The force of contact potential can be expressed as follows:

The impact of formulation ingredients on the aerosolization characteristics of spray-dried powders was examined by Rabbani NR and Seville PC. 2005; 110: 130–40; Journal of Controlled Release.

$$F_C = \frac{2\pi q^2}{A}$$

where A is the contact area (between the particle and the substrate) and charge q is produced by the detachment process from the substrate.

The integrations of the particles' opposing charges produce the Coulombic force [57].

$$F_q = k_e \frac{q^2}{d^2}$$

In this case, q, ke, and d stand for the particle's diameter, Coulomb constant, and charge.

Triboelectrification forces are produced as a result of frictional charging [68].

$$F_e = q^2 \left[1 - \frac{h}{(R^2 + h^2)^{0.5}} \right] * \frac{1}{16\pi\varepsilon_0 h^2}$$

The particles' radius, charge, distance from one another, and vacuum permittivity were denoted by R, q, h, and ε0.

1.1.1 Lift and Drag force

This force can aid in dispersing the particles and guiding them toward the targeted regions of the respiratory tract since it acts perpendicular to the airflow. The interaction between the particles and the airflow creates this force, which opposes the transport of particles through the air (Yang et al., 2010).

1.2 Mechanism of drug deposition:

1.2.1 Inertial Impaction:

Larger particle deposition is largely impacted by the physical process of inertial particle movement. When the dose is discharged through the an inhaler, rapid airflow takes place inside the cavity of the mouth. The airflow down into the airways is subjected to the particles in the released dose. The airflow is rapid in the mouth, down to the larynx, and farther down the trachea. Any particles larger than 5 μm will be deposited in the oro-pharyngeal zone.

Following gastrointestinal absorption, the medication will enter the systemic circulation when these particles are swallowed. Particles less than 5 μm reach the lungs through the wide airways and the left and right bronchus. At the bifurcation of these bigger airways, impaction deposits particles slightly below 5 μm since the airflow is still quite rapid in this area (Euliss et al., 2006).

1.2.2 Sedimentation:

The acquisition of particles smaller than 5 μm and smaller than 1 μm is caused by sedimentation, also known as "gravitational attraction," which is the second major process. The inhaled air stream becomes more slower as it passes through the constricted airways. A extremely slow-moving airflow traps the particles in the lungs' tiny airways. Gravity would cause the deposition of these particles.

The duration of the medication particles' residence in the lungs and their aerodynamic size both affect this sedimentation mechanism. The length of time spent in these more peripheral airways also increases the danger of deposition. Therefore, it is vital to do breathing maneuvers after inhaling (Horvath et al., 2012; Gritton et al., 2008).

1.2.3 Diffusion:

Very small particles, particularly those with sizes between 1μm *and 0.1-1*μm, *are mostly carried via the third mechanism, Brownian dispersion.* According to

Surendrakumar et al. (2003), Particles move by interacting with one another while floating in an extremely slow-moving air stream. If the particles collide with the airway wall, they deposit; if not, they are expelled (Hillery et al., 2001). This process is directly related to the length of the lung stay and inversely proportional to the particle size. The breath must be held once again. The overall buildup of drug particles inhaled into the lungs is significantly impacted by both strong and slow airflows. Both in the oro-pharynx and upper airways, improved deposition by inertial effect would result from increased inspirational flow. Additionally, larger inhalation volumes would allow particles to enter the lung more deeply, increasing deposition in the alveolar region.

1.3 Role of Excipients in DPI Formulation

Because they stabilize the active pharmaceutical ingredient (API), improve powder flow characteristics, and promote aerosolization, excipients are essential in DPI formulations. Typical excipients consist of:

Lactose: Lactose, the most used carrier in DPI formulations, helps to optimize flow characteristics and ensure that drug particles are distributed uniformly. Dispersion efficiency is influenced by the interaction between the medication and carrier particles.

Mannitol and Trehalose: substitute carriers that offer better stability and resistance to dampness.

Magnesium Stearate: modified particle cohesiveness and improved powder dispersibility by lubrication.

Dispersion Mechanisms in DPIs

The powder dispersion in DPIs is dependent on the device design and the patient's inhaling effort. Powder dispersion is influenced by the following mechanisms:

De-agglomeration Forces: To ensure the dispersion of fine particles, drug clumps are broken up by shear and impaction forces.

Device Resistance: The efficiency of drug dispersion is affected by the airflow velocity and turbulence caused by the internal resistance of DPIs.

Inhalation Flow Rate: Dosage delivery is influenced by patient-dependent factors. Stronger inhalation attempts are necessary for high-resistance DPIs, which may not be appropriate for all patients.

1.4 Formulation challenge for pulmonary delivery of high powder dose

A device that has been used for fifty years to treat respiratory conditions is the dry powder inhaler, which uses the active ingredient in pharmaceutical aerosols. Formoterol and fluticasone propionate are used mostly to treat respiratory diseases, with dosages ranging from 6 to 500 μg (Smith et al., 2003).

Traditional powder combinations include inert stimulants such as mannitol, sucrose, lactose, sorbitol, and glucose combined with micronized drug particles that range in size from 1 to 5 μm [83]. Currently, only pure drugs are employed to create micronized drug particles, despite particle engineering technology being a valuable tool for producing particles from a variety of primary materials. Because the drug particle is cohesive, the unoptimized powder's van der Waals forces primarily cause particle aggregation, which makes the powder challenging to disperse.

1.5 Device Design Considerations

The effectiveness of drug delivery is greatly impacted by the design of DPI devices. Important elements consist of:

Single-Dose vs. Multi-Dose DPIs: While multi-dose DPIs (like Diskus and Turbohaler) integrate pre-metered doses, which improve patient convenience, single-dose DPIs (like HandiHaler) require manual loading of medication capsules.

Airflow Path and Resistance: Optimized airflow pathways enhance turbulence and de-agglomeration of drug particles.

Dose Consistency: Accurate dose metering ensures uniform drug delivery, reducing variability in treatment outcomes.

Moisture Protection: Hygroscopic formulations require moisture-resistant packaging to prevent powder agglomeration and maintain stability.

1.6 Regulatory and Stability Considerations

Regulations established by organizations such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) must be followed by DPIs. Testing for stability assesses:

Physical and Chemical Stability: Ensures drug potency and prevents degradation over shelf life.

Moisture Sensitivity: Protects against hygroscopic changes affecting powder flow and dispersion.

Device Performance Testing: Includes dose uniformity, aerodynamic particle size distribution (APSD), and in vitro lung deposition studies.

1.7 Recent Advances in DPI Technology

Advancements in DPI design and formulation aim to enhance drug delivery efficiency and patient compliance:

Engineered Carrier Particles: Modifying carrier surface properties improves drug detachment and dispersion.

Nanoparticle-Based DPIs: Use of nanocarriers enhances bioavailability and controlled drug release.
Digital and Smart Inhalers: Integration of sensors and connectivity features enables real-time monitoring of patient inhalation patterns and adherence.

Combination Therapies: Co-formulation of multiple drugs in a single DPI for synergistic treatment of respiratory diseases.

CONCLUSION

Designing a Dry Powder Inhaler (DPI) with pharmaceutical considerations is essential for maximizing medication delivery effectiveness, guaranteeing stability, and enhancing patient outcomes. Next-generation DPIs with improved performance and adherence are the result of developments in particle engineering, excipient selection, and device innovation. The use of powder technology, such as surface coating, spray drying, and micronization, has greatly enhanced drug dispersion, flowability, and particle uniformity.

Lung deposition is improved while dosage variability is reduced by carefully regulated carrier particle shape and aerodynamic characteristics. Consistent medication emission is ensured by adjusting the cohesive and sticky forces. Additionally, advancements in powder technology facilitate the delivery of biologics and small-molecule medications, increasing the range of therapeutic uses.

In order to optimize pulmonary medication delivery, future research should concentrate on customized DPI designs that are adapted to the demands of individual patients while incorporating cutting-edge technologies. The quality of life for those suffering from respiratory disorders will be improved by ongoing developments in formulation and device optimization, which will also increase treatment effectiveness.

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