Review Article

Inhalation Performance Analysis of Dry Powder Inhaler

Muhammad Ikhmal Azhar[1], Muhammad Waseem Akram[1,2*], Idanawati Naharudin[2]

[1]Particle Design Research Group, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), 42300 Bandar Puncak Alam, Selangor, Malaysia.
[2]Non-Destructive Biomedical and Pharmaceutical Research Centre, Smart Manufacturing Research Institute, Universiti Teknologi MARA (UiTM), 42300 Bandar Puncak Alam, Selangor, Malaysia.

ABSTRACT

Dry powder inhalers (DPIs) are commonly used to treat respiratory diseases, particularly asthma, lung cancer, and chronic obstructive pulmonary disease, by delivering medications directly to the lungs. This review explores the influence of key formulation parameters such as particle size, morphology, surface roughness, and excipients on the inhalation performance and efficiency of DPIs. A comprehensive analysis of recent studies was performed to understand how these variables affect aerosolization and inhalation performance. The findings highlight that particle size is directly correlated with fine particle fraction (FPF), smaller particles (<5 µm) exhibit higher FPF (~80 %), and are suitable for targeting lower airways. Regarding morphology, elongated or needle-shaped particles experience an increased aerodynamic drag, aiding their deposition in the lower regions of the respiratory tract. In contrast, particles with smooth surfaces exhibit less interparticle adhesion and cohesion forces, leading to improved dispersion and aerosolization. Moreover, the incorporation of lubricant is shown to occupy the binding sites of the carrier, reduce agglomeration, and promote aerosolization and delivery efficiency of DPIs. In conclusion, DPIs offer strong potential to achieve targeted delivery to designated regions of the upper and lower respiratory tract through particle size modulation and formulation approaches.

Keywords: Dry powder inhaler, cascade impactor, aerosolization, particle size, inhalation

Corresponding author
Muhammad Waseem Akram
Non-Destructive Biomedical and Pharmaceutical Research Centre,
Smart Manufacturing Research Institute,
Universiti Teknologi MARA (UiTM),
42300 Bandar Puncak Alam,
Selangor, Malaysia.
Email: mwaseem.qau@gmail.com

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1.0 Introduction

The lung offers an ideal route for the local and systemic delivery of drugs. The primary function of the lung is to facilitate gas exchange, transferring oxygen from the environment into the bloodstream to maintain an adequate level of oxygen for cellular processes, including the production of adenosine triphosphate (1). Simultaneously, carbon dioxide needs to be exhaled to prevent hypercapnia. This whole process of gas exchange takes place in alveoli, which are composed of a single-cell membrane (2). Mucosal immunity is another critical function of the lung, 4-20 mm/min is the mucosal clearance rate in healthy individuals, and in a disease state, both functions are often compromised (3). The lungs are one of the few internal organs that are directly exposed to external environmental threats such as dust particles, smoke, suspended air-borne allergens, and pathogens that are responsible for various pulmonary disorders such as asthma, atelectasis, bronchitis, chronic obstructive pulmonary disease (COPD), and lung cancer that affect the functional efficiency of the lungs primarily at bronchioles and alveoli (4). According to the World Health Organization report, more than 300 million people suffer from asthma, and this figure might exceed 400 million by the end of 2025, while lung cancer accounts for the highest mortality rate (18%) (4,5).

Oral, transdermal, and parenteral routes of administration are associated with several limitations, such as the oral route is affected by harsh first-pass metabolism, the stratum corneum barrier in case of skin drug absorption, and parenteral administration may lead to premature drug degradation and leakage in blood (5). These challenges result in poor drug absorption, low bioavailability, and suboptimal pharmacological effects. Owing to the limitations of other routes, inhalation drug delivery is considered an optimal approach for the treatment of lung disorders. To treat these lung disorders variety of inhalers are available in the market, namely nebulizers, metered dose inhalers, and DPI. Among these inhalers, DPI is considered an alternative to nebulizers and metered dose inhalers owing to high stability, propellant-free nature, and ease of use (6).

1.1 Type of inhaler

In the current market, three types of inhalers are used to treat respiratory diseases. The first is a metered dose inhaler (MDI), a pressurized canister of medicine housed in a plastic holder with a mouthpiece. When sprayed, it provides a reliable, consistent dose of medication. This inhaler consists of a spacer attached to it, which facilitates the active drug reaching the target site (7). The function of the spacer is to increase the efficiency of this inhaler. Aerosol can be inhaled without the precision of time and speed, which is usually necessary. MDI disperses the drug automatically but relies on the patient to coordinate actuation of the device with inhalation. The important part in the MDI is the role of propellant, which is to provide the required pressure to atomize the drug formulation into micron-scaled droplets (8). Chlorofluorocarbons (CFCs), usually used as the propellant of MDI, are found to deplete the ozone layer high above the earth (9). Alternative devices have been developed to replace the CFC propellant in MDI, with hydrofluoroalkane (HFA) selected as a substitute for CFCs. CFCs are extremely potent global warming agents as well as harmful to the ozone layer. They are replaced by HFAs, which, though harmless to the ozone layer, still have a global warming potential more than 1000 times that of carbon dioxide (9).

The second inhaler is a nebulizer or also known as a soft mist inhaler. A nebulizer is a machine that sprays a fine, liquid mist of

medicine. The medicine is delivered with a mouthpiece or mask (10). Nebulizers are often used by people who cannot use MDI, such as infants and young children, and people with severe asthma. An air compressor helps to convert liquid medicine into a mist, which travels through a tube that connects to a mouthpiece. Nebulized treatment provides patients with an alternative administration route that avoids the need for inspiratory flow, manual dexterity, or complex hand-breath coordination (10). The last one is DPIs, DPI formulations are generally composed of drug substance, fine or coarse carrier, and lubricant. DPI devices are further classified into two types, namely multiple-dose devices and single-dose devices. The single-dose device needs to have a capsule placed in the device immediately before each treatment (9). For DPIs to de-aggregate (break up) the powder in the device and disseminate (transport the drug into the lung), the patient must produce the proper inspiratory flows. Some patients struggle to acquire enough inhalation flows since each DPI on the market has a different inspiratory flow requirement to activate powder de-aggregation and enable optimal lung delivery. The advantages of DPIs are formulation stability, propellant-free, small, portable, quick to use, and no need for a spacer (11). DPI mainly comprises particles in the solid state, which are powder. It offers superior physicochemical stability relative to the liquid state and MDI, of which the formulation consists of propellant and cosolvents. As the inhalation of DPI is based on the inhalation flow rate of the patient, it does not require propellant to create the aerosolized spray of medicine (12). This propellant-free approach will lead to environmental sustainability.

1.2 Dry powder inhaler

Nowadays, DPIs are commonly utilized for delivering medication directly to the respiratory system, particularly in the management of asthma and lung cancer. The effectiveness of DPIs in delivering medication depends not only on the formulation of the drug but also on the inhalation technique of the patients. However, in this study, the human factor has been excluded and focuses more on the DPI performances. Understanding the inhalation performance of DPIs is crucial for optimizing drug delivery and ensuring successful therapy outcomes.

The evaluation of DPI inhalation performance involves a comprehensive assessment of several critical parameters, including FPF, emitted dose, aerodynamic particle size distribution (PSD), and deposition patterns in the respiratory tract. To assess the inhalation performance of particles, a mechanical simulation of the human respiratory tract, the Cascade Impactor, is widely used (13). Its stages are useful for separating the particle fraction with varying aerodynamic diameter ranges. The inhalation properties adopted were emitted dose (ED), FPF, and extra-fine particle fraction (eFPF). ED represents the proportion of powder that can be released from the capsule and is suppressed by static charges, which trap tiny particles inside the capsule against the inhalation flow (14). Meanwhile, FPF is important for assessing the inhalation properties of general DPI formulations, as it provides the proportion of fine particles with diameters <5 μm (15). Certainly, there are also other aspects when it comes to the performance of DPI products. Customizing the aerodynamic properties of DPI formulations is essential for delivery to the deep lung.

1.3 Aerosolization and inhalation attributes of DPI

Ensuring the appropriate aerodynamic properties of DPI formulations is crucial for achieving effective drug delivery to the deeper regions of the lungs, which also require careful consideration of factors such as surface morphology, particle shape, crystallinity, and excipient used in the formulation (16). Excipients play a critical role in improving the dispersibility and flow characteristics of the powder, thereby influencing the aerodynamic behavior and deposition pattern within the respiratory tract. Carefully selecting suitable excipients can significantly enhance the aerosolization efficiency, optimize drug targeting to the intended lung regions, and minimize the potential for undesirable side effects (17).

Excipients used in DPIs are generally recognized as safe by the Food and Drug Administration and are known to enhance powder dispersibility while aiding particle de-aggregation (18). Its presence in the formulation promotes the formation of cohesive bonds between drug particles, improving their flow properties and reducing the likelihood of particle aggregation during inhalation (16,18). Lubricants are commonly used in pharmaceutical formulations to improve the flowability of powder by reducing interparticle friction (19,20).

Considering the impact of excipients on DPI performance is essential for tailoring formulations to achieve optimal drug delivery. The analysis of inhalation performance in dry DPIs presents challenges that primarily revolve around the intricate interplay between formulation characteristics, device design, and the aerodynamic behavior of drug particles. The use of DPI has been prioritized compared to the other types of inhalers owing to their superior physicochemical stability in contrast to nebulizers and MDI (12). However, one significant challenge in studying inhalation performance analysis in DPIs lies in the complexity of the formulation parameters. Factors such as particle size distribution, surface morphology, shape, and crystallinity significantly influence the aerosolization process and subsequent drug deposition within the respiratory tract. Additionally, device-related factors play a pivotal role in inhalation performance. The design of the inhaler, including the geometry, airflow resistance, and mechanism of drug dispersion, influences the generation of the aerosol and the drug's ultimate deposition in the lungs.

The objective of this research is to investigate the characteristics and physicochemical properties of DPI formulations and their relationship with aerosolization and inhalation performances. The findings of this study will provide valuable background data to assist researchers in designing improved dry powder formulations for enhanced pulmonary drug delivery.

2.0 Method

Initially, both research and review articles focusing on inhalation studies were examined using multiple databases such as Science Direct, Google Scholar, National Library of Medicine (PubMed), Springer link, Research Gate, Elsevier, and Liebert Pub. Data from studies (n = 90) that primarily focused on dry powder inhalation were included in this study, with the majority of data obtained from sources published between 2001-2024. The keywords and terms used during the search of the data such as dry powder inhaler, pulmonary drug delivery, inhalation, aerosolization, particle size, and morphology. Figure 1 illustrates the sequential steps undertaken to accomplish the objectives of this study. The primary objective of this study is to evaluate specific physicochemical

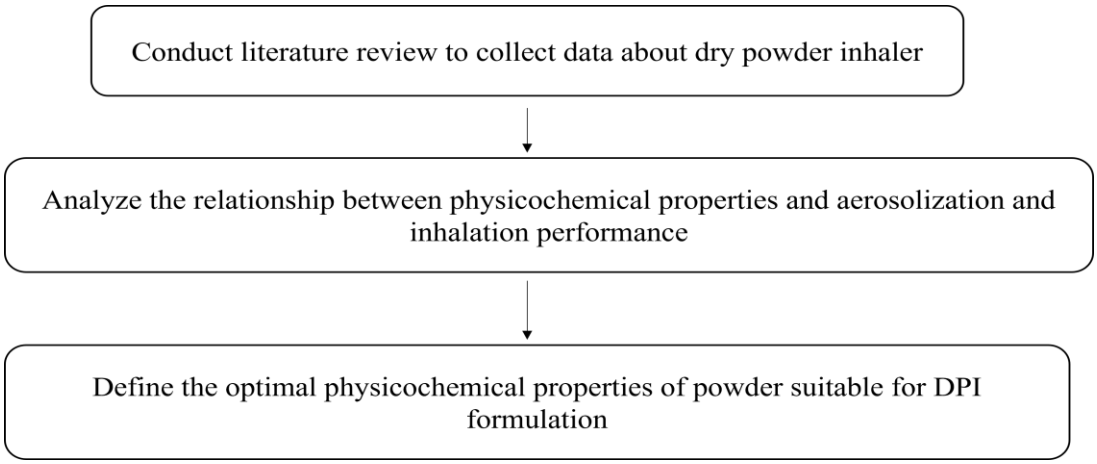

Figure 1: Research methodology approach for the analysis of the dry powder inhaler.

attributes, such as particle size, morphology, and surface roughness of the dry powder, which may significantly impact aerosolization and inhalation performances. This evaluation process involves several steps, such as examining the influence of particle size on aerosolization efficiency and deposition within the respiratory system. The potential impact of particle morphology on aerosolization performance and lung deposition is also investigated. Moreover, surface roughness and excipients' effects on aerosolization and inhalation efficiency are also envisaged. This knowledge will contribute to optimizing the formulation and development of inhalation therapies by considering factors that affect aerosolization and inhalation performance.

3.0 Results and discussion

3.1 Effect of particle size

In general, smaller particle sizes tend to exhibit higher FPF values, indicating better aerosolization and improved targeting of the drug to the desired site (21). This correlation can be attributed to the increased likelihood of smaller particles remaining suspended in the airstream, overcoming gravitational settling and reaching the lower airways. These particles can effectively penetrate the respiratory system's narrow air passages, leading to increased FPF values (21). Conversely, larger particles have a greater tendency to deposit in the upper respiratory tract, resulting in lower FPF values. These larger particles may be subject to impaction or sedimentation, limiting their ability to reach the intended site of action within the lungs (22). There are three mechanisms governing particle deposition in the lung airways. The first one is inertial impaction, which involves the deposition of large particles in the oropharyngeal and large airways. These particles are unable to follow the directional changes of the inspired airstream, particularly in the oropharynx and at airway bifurcations. Loss of drugs by inertial impaction in the oropharynx is the biggest hurdle for lung deposition with passive dry powder devices (21). Thus, the loss of drug due to inertial impaction in the oropharynx is a major hurdle to achieving lung deposition using a passive dry powder device (23). The second mechanism is gravitational sedimentation, which usually affects small particles in the size range of 2–

6 µm. It occurs in the small conducting airways where the airflow velocity is slow (24). The third mechanism is diffusion, which involves small particles (<2µm) that rely on Brownian motion. This mechanism is important in the small airways and alveoli, where the airflow is negligible (22).

The PSD of the DPI formulations was analyzed by cascade impaction analysis (16). Cascade impactors work on the principle of inertial impaction (25). As an aerosol passes through the impactor, particles with different sizes and velocities are subjected to centrifugal forces and inertial impaction on a series of collection plates or stages. Larger particles with higher inertia are collected at the beginning stages, while smaller particles continue to travel and are collected at subsequent stages. The particle size distribution and deposition characteristics can be determined by analyzing the collected particles at each stage.

The cascade impactor consists of several stages, typically arranged in a series of decreasing size or increasing cut-off aerodynamic diameters (26). Each stage contains a collection plate or surface, which captures particles of specific sizes. The aerosol sample is drawn through the impactor using a controlled airflow rate, ensuring that particles are impacted and deposited on the collection plates based on their aerodynamic behavior.

3.1.1 Correlation between particle size and FPF

Particle size D_{50} is defined as the diameter at which 50% of the particles in a distribution are smaller and 50% are larger (27). Upon reviewing the data, a diverse range of particle sizes was found that were utilized for pulmonary delivery, ranging approximately from 0.3 µm to 14.72 µm (Figure 2). Smaller particle sizes, such as those below 5 µm, have a higher probability of reaching the deep lung regions due to their improved aerodynamic properties. The correlation data presented in Figure 2 provides evidence that particles within this desired size range, favorable for effective lung deposition and targeted drug delivery (28–97).

FPF was found to be promising with smaller particles, where the drug deposits in the lower areas of the lungs, as shown in Figure 2 (31). Hyaluronic acid-based aggregated nanoparticles having a size of < 5µm expressed better drug deposition in the alveolar region (31), while meloxicam formulation, owing to larger particles, exhibited poor aerodynamic properties and deposited in the extrathoracic spaces (29). Samples with a larger particle size demonstrated lower FPF value, and the following equation is utilized for FPF calculation (98).

FPF=Fine particle dose/emitted dose x 100

The correlation demonstrates a significant relationship between particle size and FPF. A higher FPF value suggests a higher proportion of fine particles capable of reaching the desired target site within the lungs, while a lower FPF value indicates a larger fraction of particles that may deposit in the oropharyngeal region or fail to penetrate deeply into the respiratory tract, as shown in Figure 2 (32). Findings of a recent study exhibited that smaller-sized microcarriers (d50: around 5 µm) improved the FPF (43.47 ± 3.25 %) by delivering nanoparticles into the deeper region of the lungs (99).

3.1.2 Correlation between PSD and FPF

Particle size distribution describes the range of particle sizes present in a given sample or formulation. It provides information about the relative proportions of particles across different size ranges. PSD can be calculated by using the formula $(d_{90}-d_{10}) / d_{50}$ (100). A

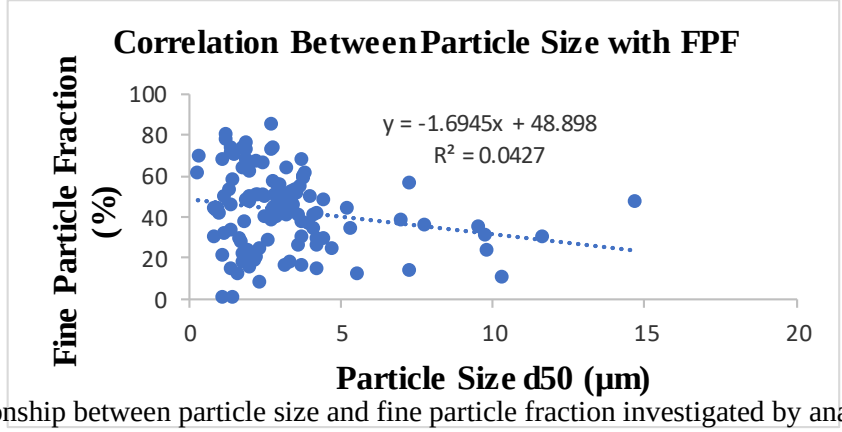

Figure 2: Relationship between particle size and fine particle fraction investigated by analyzing various studies (28-97)

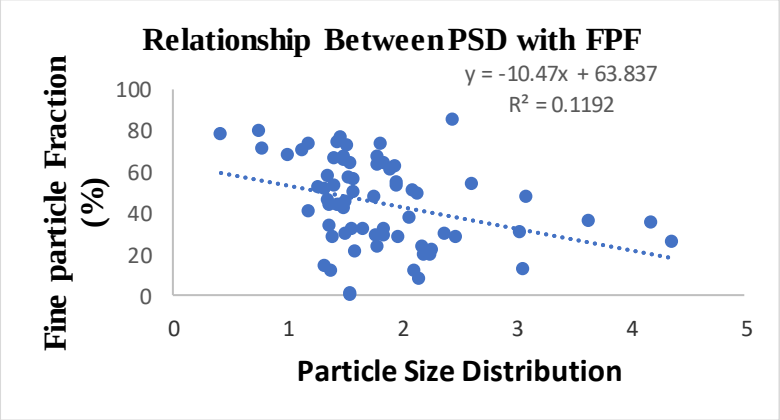

Figure 3: Relationship between the particle size distribution and fine particle fraction determined through analysis of various studies (28-97)

narrow and well-controlled size distribution ensures a significant proportion of particles within the desired size range for optimal deposition in the lungs. Formulations with a higher concentration of fine particles tend to yield a higher FPF due to their improved ability to bypass the upper airways and reach the lower lung regions, as shown in Figure 3. In the study involving Colistin and Meropenem (101), particles exhibited a narrow size distribution (1.55 µm), representing a high degree of uniformity in particle size, which resulted in the higher FPF of 80%.

3.2 Effect of particle morphology

Particle shape plays a significant role in determining the aerosol properties of DPIs. Irregularly shaped particles tend to experience greater air resistance and have reduced aerodynamic efficiency. Meanwhile, non-spherical particles may exhibit altered deposition patterns within the respiratory tract (46). Typically, particle shape affects the inter-particulate interactions within the powder formulation. Irregularly shaped particles may have more complex surface geometries, leading to variations in adhesive and cohesive forces between particles (34).

These interactions impact powder flowability, dispersibility, and the ability to aerosolize the powder upon inhalation, which prevents it from de-aggregation in the upper respiratory tract. However, when compared with spherical shape, it can exhibit minimal inter-particulate interactions within the formulation, as its smooth surface allows for easy separation and dispersion (102). This reduced cohesion and agglomeration lead to improved flowability and dispersibility of spherical particles. As a result, a larger proportion of spherical particles can be effectively released from the inhaler device, increasing the likelihood of their deposition. Therefore, the spherical shape provides particles with easy detachment, which is suitable for drug delivery to the upper lung (103). On the other hand, irregular particles can experience enhanced inertial impaction and gravitational sedimentation due to their non-uniform shape. The irregularities in particle shape can cause changes in the aerodynamic behavior and settling trajectory velocity, leading to increased deposition in the desired lung regions (51,83). This can contribute to a higher FPF, particularly for particles that tend to deposit in the lower airways or alveolar region.

Elongated particles can significantly influence aerosol properties due to their distinct shape characteristics. Elongated particles experience different aerodynamic behavior compared to the other shapes. Their elongated shape introduces asymmetry, leading to changes in drag forces and particle orientation in the airflow (20). The non-spherical shape can result in different flow patterns, eddies, and vortex shedding, affecting particle transport and deposition (Figure 4). The unique shape of elongated particles offers the potential for targeted delivery to specific lung regions. By manipulating the aspect ratio and surface properties of elongated particles, it can optimize the behavior for deposition in specific areas, such as the deep lung or targeted sites for drug absorption (50). This can be advantageous for delivering medications to treat conditions affecting specific regions of the respiratory system. Elongated particles increase particle-particle and particle-device interactions compared to spherical particles. Their elongated shape can lead to entanglement, alignment, or bridging between particles, resulting in altered powder flow properties (48). Moreover, elongated particles may have different contact areas and adhesive forces when interacting with the inhaler device or carrier particles, influencing their detachment and aerosolization efficiency.

In the recent study, the particles with irregular or needle-shaped exhibited reduced internal friction and better dispersion performance in the air when compared with spherical-shaped particles (88). Needle-shaped carrier particles generally have a high elongation rate, which allows drug deposition in the small airways, resulting in more effective drug deposition in the lung (22). Carriers having a higher elongation rate (5.89 ± 0.2) expressed more deposition of salbutamol into the lower lung region (104). These carrier particles provide a higher FPF and reduce drug loss, especially at low flow rates. Therefore, needle-like or elongated-shaped carriers are considered a suitable choice due to their high dispersibility and high FPF values.

3.3 Effect of surface roughness

Surface roughness of particles can significantly influence aerosol properties in the DPI. The surface roughness of particles can impact their dispersibility and aerosolization behavior, as shown in Figure 5. Rough surfaces introduce irregularities and asperities that increase interparticle friction and cohesion (44). This can lead to agglomeration, poor dispersion, and hurdles

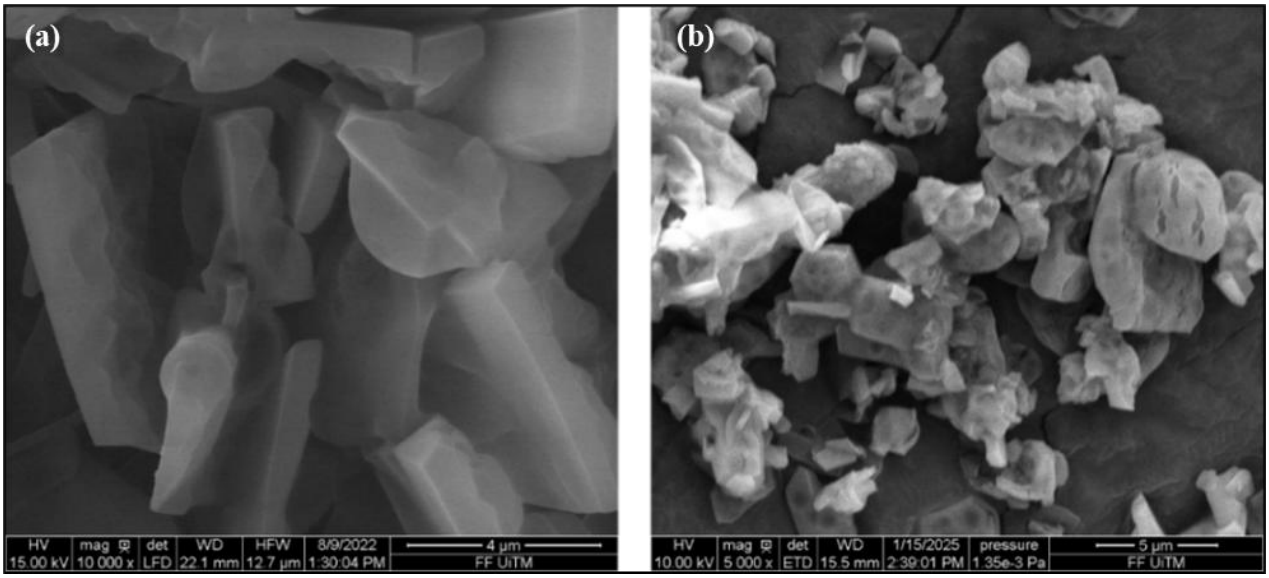

Figure 4: Scanning electron morphology of two different variants of non-spherical shaped lactose-based inhalation carrier (a) coarse carrier (particle size >5µm) and (b) fine carrier (particle size <5µm).

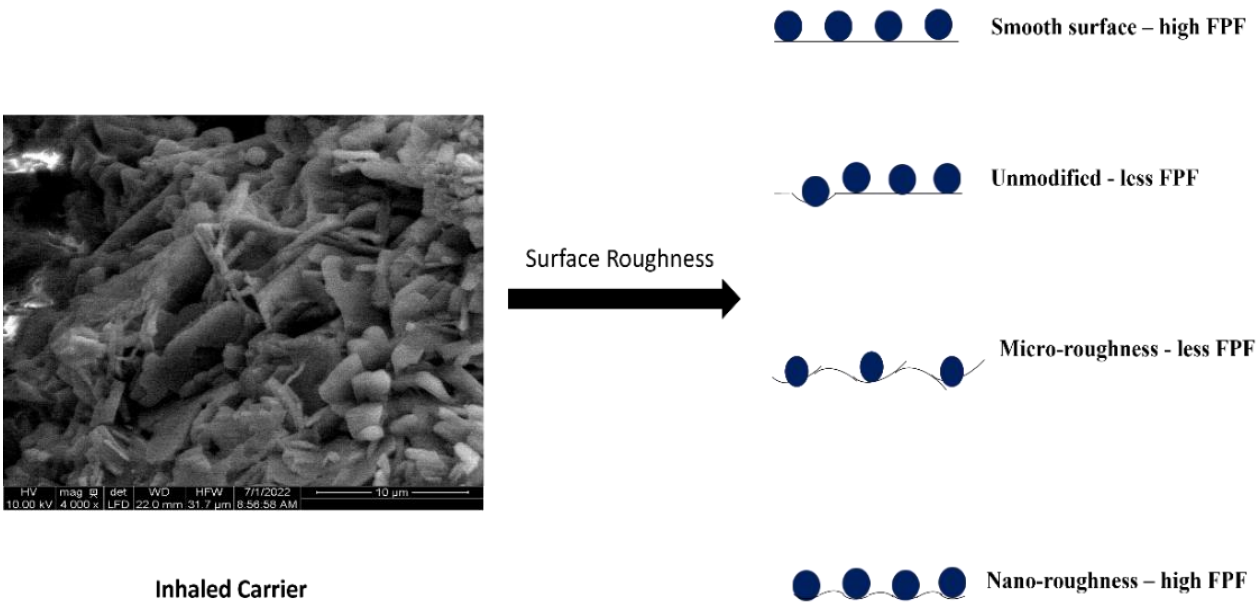

Figure 5: Effect of carrier surface roughness on fine particle fraction.

in achieving consistent and efficient aerosolization. Smoother surfaces, on the other hand, promote better flowability and dispersibility, allowing for improved aerosol generation and drug delivery (36). A smooth surface is generally useful to target the drug to the lower region of the lungs, as the drug can easily detach due to less adhesive forces (Figure 5). Surface roughness influences particle-particle interactions, while rough surfaces provide more contact points and interlocking regions within the formulation (14,105).

The surface roughness of particles can influence their deposition pattern within the respiratory tract. Rough surfaces tend to experience more frequent and stronger interactions with the airway walls, leading to increased deposition in the upper airways (e.g., oropharynx) rather than reaching the

targeted regions in the deep lung (29). Smoother surfaces have reduced wall adhesion, enabling particles to penetrate deeper into the lung, increasing the chances of deposition in the desired regions.

Surface roughness can also affect the stability of aerosol particles. Rough surfaces may be more prone to moisture absorption, leading to particle growth, agglomeration, and decreased stability. However, in the recent study, the stability of the particles whose surface has been modified by trileucine showed a clear dependence on the surface rugosity of the suspended particles of which more corrugated particles lead to more stable suspensions, and all of them are more stable than those made of pure trehalose particles with relatively smooth surfaces (106,107). However, further studies should be performed to provide a detailed explanation regarding the stability of the particles with surface roughness.

3.4 Effect of excipient

Excipients in DPI formulations play a crucial role in influencing the inhalation performance. Magnesium stearate is a commonly used lubricant in DPI formulations. Its main role is to improve the flow properties of the powder, reducing cohesive forces by occupying the binding site at large carrier and enhancing powder dispersibility. The addition of excipients such as magnesium stearate is useful when the DPI formulation consists of a large carrier to increase drug flowability (33). This action leads to easy detachment of drug particles during aerosolization (19). Inclusion of 5% magnesium stearate in DPI formulation improved aerosolization by reducing particle agglomeration (108).

Mannitol is a commonly used excipient in DPI formulations due to its excellent flowability and low hygroscopicity. It acts as a bulking agent and facilitates the dispersion of active pharmaceutical ingredients within the powder matrix (42). Mannitol also enhanced the flow properties of the powder, ensuring consistent and efficient aerosol generation. Leucine is an amino acid excipient used as a dispersibility enhancer in DPI formulations. It helps to improve the dispersion and deagglomeration of powder particles by promoting fine particle formation (103). Particles prepared using l-leucine through the spray drying technique resulted in higher FPF (66.6 %) (109). Leucine was used to prepare salvianolic acid (SAL) DPI by the spray drying method, which improved the powder flow properties, drug delivery efficiency, in vitro deposition effect of SAL-DPI, and enhanced its moisture resistance. However, the composition of leucine is important in the formulation of the drug substance (33,44). The presence of leucine provides better particle size distribution and has a high fine particle fraction among others. Leucine acts as a surface-active agent, reducing particle cohesion and facilitating the separation of individual particles during inhalation (17). Sucrose is used as a carrier or filler excipient in DPI formulations to improve the powder flow and enhance dispersibility (61). Sucrose also provides stability to the formulation and can contribute to the preservation of the drug's chemical integrity. However, there is insufficient data regarding the advantage of sucrose in the DPI formulation.

Chitosan is a biopolymer excipient with mucoadhesive properties. In DPI formulations, chitosan is used as a coating material to enhance particle adhesion to the respiratory epithelium, prolonging drug residence time and promoting targeted drug delivery (79,82,110). Chitosan can also improve powder flowability and reduce particle aggregation. Thiolated chitosan (TC) is a modified form of chitosan, it possesses enhanced mucoadhesive properties. TC can form reversible disulfide bonds with mucus,

improving the adhesion of particles to the airway surfaces. TC improved the cellular permeation properties of hyaluronic acid (31). Nanoparticles fabricated with TC exhibited dual functionality by enhancing epithelial permeation and enabling controlled drug release. The thiol-reacted biomolecules also show enhanced cellular uptake of the particles and have the potential to localize at the target (31). Chitosan-based nanoparticles, owing to their positively charged surface, interact with negatively charged mucus, leading to enhanced penetration (111).

Dipalmitoylphosphatidylcholine (DPPC) is a phospholipid excipient commonly used in DPI formulations. It acts as a surfactant and can improve the dispersibility and flow properties of the powder. DPPC can enhance the fluidization of the powder, reducing particle agglomeration and promoting the generation of fine particles suitable for inhalation (49). Polyvinyl alcohol (PVA) is a water-soluble excipient that can be used as a dispersing agent in DPI formulations (57). It improves the wettability and dispersibility of the powder, facilitating the formation of a homogeneous aerosol cloud upon inhalation. PVA also enhances the flow properties of the powder, promoting efficient aerosolization. Phytoglycogen is a natural excipient derived from plants. Phytoglycogen is used in the formulation to act as an excipient matrix. It provides a large hydrodynamic particle diameter distribution (14). This matrix-based formulation provides a platform for an active pharmaceutical ingredient to embed or attach. This formulation leads to improved drug mobility and distribution. Phytoglycogen has excellent film-forming properties, which can contribute to the formation of a cohesive powder matrix, reducing particle aggregation and enhancing the stability of the formulation.

4.0 Conclusion

Dry powder inhalers are widely used for the treatment of respiratory diseases. The effectiveness of DPIs in delivering medication depends on various factors, including particle size, morphology, roughness, and incorporation of excipients. Smaller particle sizes, particularly those below 5 μm, have higher FPF and are more likely to reach the deep lung regions. PSD analysis using cascade impactors helps evaluate the aerodynamic properties of DPI formulations. Irregular particles are more susceptible to inertial impaction and gravitational sedimentation due to their shape asymmetry. The irregularities in particle shape can lead to changes in aerodynamic behavior and settling trajectory velocity, resulting in increased deposition in the desired lung regions. Surface roughness affects powder flowability and cohesive forces, with smoother surfaces enhancing aerosolization and drug delivery. Excipients such as magnesium stearate, mannitol, leucine, and chitosan are essential for enhancing flow properties, dispersibility, and mucoadhesion. These functionalities contribute to enhanced aerosol generation, powder stability, and targeted drug delivery.

Optimized DPI formulations have the potential to enhance particle dispersion, deposition, and lung targeting, leading to improved drug absorption, bioavailability, and better disease management. Further research and development efforts should focus on tailoring the aerodynamic properties of DPI formulations, selecting appropriate excipients, and optimizing powder characteristics to enhance inhalation performance and maximize efficiency, effectiveness, and patient adherence of DPI therapy.

Authorship contribution statement

MIBA: Writing - original draft, validation, formal analysis, data curation. **MWA:** Validation, formal analysis, conceptualization, methodology, supervision, writing – review and editing. **IN:** Writing – review and editing**.**

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Conflict of Interest

Authors declare no conflict of interest in the present work.

References

1. Patel S, Miao JH, Yetiskul E, Anokhin A, Majmundar SH. Physiology, Carbon Dioxide Retention. StatPearls; 2022.

2. Knudsen L, Ochs M. The micromechanics of lung alveoli: Structure and function of surfactant and tissue components. Histochem Cell Biol. 2018;150:661–676.

3. Bailey KL. Aging diminishes mucociliary clearance of the lung. Adv Geriatr Med Res. 2022;4(2):1–11.

4. Akram MW, Wong TW. Translational hurdles in anti-asthmatic nanomedicine development. Expert Opin Drug Deliv. 2024;21(7):987–9.

5. Iskandar A, Kim SK, Wong TW. "Drug-Free" chitosan nanoparticles as therapeutic for cancer treatment. Polym Rev. 2024;64(3):818–71.

6. Shetty N, Cipolla D, Park H, Zhou QT. Physical stability of dry powder inhaler formulations. Expert Opin Drug Deliv. 2020;17(1):77–96.

7. Harris G. What type of inhalers are available for patients with asthma. Br J Health Care Manag. 2019;25(11):314–7.

8. Kar M, Chourasiya Y, Maheshwari R, Tekade RK. Current developments in excipient science: Implication of quantitative selection of each excipient in product development. In: Basic Fundamentals of Drug Delivery. Elsevier; 2018:29–83.

9. Keeley D, Scullion JE, Usmani OS. Minimising the environmental impact of inhaled therapies: Problems with policy on low carbon inhalers. Eur Respir J. 2020;55.

10. Barjaktarevic IZ, Milstone AP. Nebulized therapies in COPD: Past, present, and the future. Int J Chron Obstruct Pulmon Dis. 2020; 15:1665–77.

11. Wu X, Li X, Mansour HM. Surface analytical techniques in solid-state particle characterization for predicting performance in dry powder inhalers. Kona Powder Part J. 2010; 28:3-19.

12. Dal Negro RW. Dry powder inhalers and the right things to remember: A concept review. Multidiscip Respir Med. 2015;10.

13. Elia A, Cocchi M, Cottini C, Riolo D, Cafiero C, Bosi R, *et al*. Multivariate data analysis to assess dry powder inhalers performance from powder properties. Powder Technol. 2016;301:830–8.

14. Tse JY, Kadota K, Imakubo T, Uchiyama H, Tozuka Y. Enhancement of the extra-fine particle fraction of levofloxacin embedded in excipient matrix formulations for dry powder inhaler using response surface methodology. Eur J Pharm Sci. 2021;1:156.

15. Hickey AJ, Martonen TB, Yang Y. Pharmaceutica acta helvetiae Theoretical relationship of lung deposition to the fine particle fraction of inhalation aerosols. Pharm Acta Helv. 1996;7.

16. Xu Y, Harinck L, Lokras AG, Gerde P, Selg E, Sjöberg CO, *et al*. Leucine improves the aerosol performance of dry powder inhaler formulations of siRNA-loaded nanoparticles. Int J Pharm. 2022;10:621.

17. Shetty N, Park H, Zemlyanov D, Mangal S, Bhujbal S, Zhou Q. Influence of excipients on physical and aerosolization stability of spray dried high-dose powder formulations for inhalation. Int J Pharm. 2018;544(1):222–34.

18. Schoubben A, Vivani R, Paolantoni M, Perinelli DR, Gioiello A, Macchiarulo A, *et al*. D-leucine microparticles as an excipient to improve the aerosolization performances of dry powders for inhalation. Eur J Pharm Sci. 2019;130:54–64.

19. Kumar V, Sethi B, Yanez E, Leung DH, Ghanwatkar YY, Cheong J, *et al*. Effect of magnesium stearate surface coating method on the aerosol performance and permeability of micronized fluticasone propionate. Int J Pharm. 2022;5;615.

20. Kaialy W, Nokhodchi A. The use of freeze-dried mannitol to enhance the in vitro aerosolization behaviour of budesonide from the Aerolizer®. Powder Technol. 2016; 288:291–302.

21. Yang MY, Chan JGY, Chan HK. Pulmonary drug delivery by powder aerosols. J Control Release. 2014;193:228–40.

22. Peng T, Lin S, Niu B, Wang X, Huang Y, Zhang X, *et al*. Influence of physical properties of carrier on the performance of dry powder inhalers. Acta Pharm Sin B. 2016;6:308–18.

23. Darquenne C. Aerosol deposition in the human lung in reduced gravity. J Aerosol Med Pulm Drug Deliv. 2014;27:170–7.

24. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: Physiological factors affecting therapeutic effectiveness of aerosolized medications. Br J Clin Pharmacol. 2003;56:588–99.

25. Marek SR, Donovan MJ, Smyth HDC. Effects of mild processing pressures on the performance of dry powder inhaler formulations for inhalation therapy (1): Budesonide and lactose. Eur J Pharm Biopharm. 2011;78(1):97–106.

26. Traini D, Scalia S, Adi H, Marangoni E, Young PM. Polymer coating of carrier excipients modify aerosol performance of adhered drugs used in dry powder inhalation therapy. Int J Pharm. 2012;438(1–2):150–9.

27. Donovan MJ, Smyth HDC. Influence of size and surface roughness of large lactose carrier particles in dry powder inhaler formulations. Int J Pharm. 2010;402:1–9.

28. Ye Y, Ma Y, Fan Z, Zhu J. The effects of grid design on the performance of 3D-printed dry powder inhalers. Int J Pharm. 2022;5:627.

29. Chvatal A, Farkas Á, Balásházy I, Szabó-Révész P, Ambrus R. Aerodynamic properties and in silico deposition of meloxicam potassium incorporated in a carrier-free DPI pulmonary system. Int J Pharm. 2017;520(1–2):70–8.

30. Almeida LC, Bharadwaj R, Eliahu A, Wassgren CR, Nagapudi K, Muliadi AR. Capsule-Based dry powder inhaler evaluation using CFD-DEM simulations and next generation impactor data. Eur J Pharm Sci. 2022;1:175.

31. Mukhtar M, Pallagi E, Csóka I, Benke E, Farkas Á, Zeeshan M, *et al*. Aerodynamic properties and in silico deposition of isoniazid loaded chitosan/thiolated chitosan and hyaluronic acid hybrid nanoplex DPIs as a potential TB treatment. Int J Biol Macromol. 2020;165:3007–19.

32. Li J, Ma S, Sun Y, Song R, Cai B, Li H, et al. Predicting in vitro lung deposition behavior of combined dry powder inhaler via rheological properties. Eur J Pharm Biopharm. 2022;181:195–206.

33. Rashid MA, Muneer S, Mendhi J, Sabuj MZR, Alhamhoom Y, Xiao Y, *et al*. Inhaled Edoxaban dry powder inhaler formulations: Development,characterization and their effects on the coagulopathy associated with COVID-19 infection. Int J Pharm. 2021;25;608.

34. Muneer S, Wang T, Rintoul L, Ayoko GA, Islam N, Izake EL. Development and characterization of meropenem dry powder

inhaler formulation for pulmonary drug delivery. Int J Pharm. 2020;25;587.

35. Xu Y, Harinck L, Lokras AG, Gerde P, Selg E, Sjöberg CO, *et al*. Leucine improves the aerosol performance of dry powder inhaler formulations of siRNA-loaded nanoparticles. Int J Pharm. 2022;10;621.

36. Kumar V, Sethi B, Yanez E, Leung DH, Ghanwatkar YY, Cheong J, *et al*. Effect of magnesium stearate surface coating method on the aerosol performance and permeability of micronized fluticasone propionate. Int J Pharm. 2022;5:615.

37. Shiehzadeh F, Hadizadeh F, Mohammadpour A, Aryan E, Gholami L, Tafaghodi M. Streptomycin sulfate dry powder inhalers for the new tuberculosis treatment schedule. J Drug Deliv Sci Technol. 2019;52:957–67.

38. Chennakesavulu S, Mishra A, Sudheer A, Sowmya C, Suryaprakash Reddy C, Bhargav E. Pulmonary delivery of liposomal dry powder inhaler formulation for effective treatment of idiopathic pulmonary fibrosis. Asian J Pharm Sci. 2018;13(1):91–100.

39. Zhang X, Zhao Z, Cui Y, Liu F, Huang Z, Huang Y, *et al*. Effect of powder properties on the aerosolization performance of nanoporous mannitol particles as dry powder inhalation carriers. Powder Technol. 2019;358:46–54.

40. McShane PJ, Weers JG, Tarara TE, Haynes A, Durbha P, Miller DP, *et al*. Ciprofloxacin Dry Powder for Inhalation (ciprofloxacin DPI): Technical design and features of an efficient drug–device combination. Pulm Pharmacol Ther. 2018;50:72–9.

41. Sun Y, Cui Z, Sun Y, Qin L, Zhang X, Liu Q, *et al*. Exploring the potential influence of drug charge on downstream deposition behaviour of DPI powders. Int J Pharm. 2020; 15:588.

42. Wu HT, Su YC, Wang YM, Tsai HM. Characterization and aerosolization performance of mannitol particles produced using supercritical assisted atomization. Chem Eng Res Des. 2018;137:308–18.

43. Thalberg K, Ahmadi R, Stuckel J, Elfman P, Svensson M. The match between adhesive mixture powder formulations for inhalation and the inhaler device. Eur J Pharm Sci. 2023 ;186:106457.

44. Prota L, Santoro A, Bifulco M, Aquino RP, Mencherini T, Russo P. Leucine enhances aerosol performance of Naringin dry powder and its activity on cystic fibrosis airway epithelial cells. Int J Pharm. 2011;412(1–2):8–19.

45. Schoubben A, Vivani R, Paolantoni M, Perinelli DR, Gioiello A, Macchiarulo A, *et al*. D-leucine microparticles as an excipient to improve the aerosolization performances of dry powders for inhalation. Eur J Pharm Sci. 2019;130:54–64.

46. Ke WR, Kwok PCL, Khanal D, Chang RYK, Chan HK. Co-spray dried hydrophobic drug formulations with crystalline lactose for inhalation aerosol delivery. Int J Pharm. 2021;602.

47. Traini D, Scalia S, Adi H, Marangoni E, Young PM. Polymer coating of carrier excipients modify aerosol performance of adhered drugs used in dry powder inhalation therapy. Int J Pharm. 2012;438(1–2):150–9.

48. Kaialy W, Martin GP, Ticehurst MD, Momin MN, Nokhodchi A. The enhanced aerosol performance of salbutamol from dry powders containing engineered mannitol as excipient. Int J Pharm. 2010;392(1–2):178–88.

49. Cuvelier B, Eloy P, Loira-Pastoriza C, Ucakar B, Sanogo AA, Dupont-Gillain C, et al. Minimal amounts of dipalmitoylphosphatidylcholine improve aerosol performance of spray-dried temocillin powders for inhalation. Int J Pharm. 2015;495(2):981–90.

50. Kaialy W, Alhalaweh A, Velaga SP, Nokhodchi A. Influence of lactose carrier particle size on the aerosol performance of budesonide from a dry powder inhaler. Powder Technol. 2012;227:74–85.

51. Mangal S, Park H, Zeng L, Yu HH, Lin YW, Velkov T, *et al*. Composite particle formulations of colistin and meropenem with

improved in-vitro bacterial killing and aerosolization for inhalation. Int J Pharm. 2018;548(1):443–53.

52. Karner S, Littringer EM, Urbanetz NA. Triboelectrics: The influence of particle surface roughness and shape on charge acquisition during aerosolization and the DPI performance. Powder Technol. 2014;262:22–9.

53. Meenach SA, Anderson KW, Hilt JZ, McGarry RC, Mansour HM. Characterization and aerosol dispersion performance of advanced spray-dried chemotherapeutic PEGylated phospholipid particles for dry powder inhalation delivery in lung cancer. Eur J Pharm Sci. 2013;49(4):699–711.

54. Kaialy W, Nokhodchi A. Dry powder inhalers: Physicochemical and aerosolization properties of several size-fractions of a promising alternative carrier, freeze-dried mannitol. Eur J Pharm Sci. 2015;68:56–67.

55. Mangal S, Park H, Nour R, Shetty N, Cavallaro A, Zemlyanov D, *et al*. Correlations between surface composition and aerosolization of jet-milled dry powder inhaler formulations with pharmaceutical lubricants. Int J Pharm. 2019;568:118507.

56. Shetty N, Park H, Zemlyanov D, Mangal S, Bhujbal S, Zhou QT. Influence of excipients on physical and aerosolization stability of spray-dried high-dose powder formulations for inhalation. Int J Pharm. 2018;544(1):222–34.

57. Pomázi A, Ambrus R, Szabó-Révész P. Physicochemical stability and aerosolization performance of mannitol-based microcomposites. J Drug Deliv Sci Technol. 2014;24:172–8.

58. Shariare MH, De Matas M, York P. Effect of crystallisation conditions and feedstock morphology on the aerosolization performance of micronised salbutamol sulphate. Int J Pharm. 2011;415(1–2):62–72.

59. Kho K, Hadinoto K. Optimizing aerosolization efficiency of dry-powder aggregates of thermally-sensitive polymeric nanoparticles produced by spray-freeze-drying. Powder Technol. 2011;214(1):169–76.

60. Lin L, Quan G, Peng T, Huang Z, Singh V, Lu M, *et al*. Development of fine solid-crystal suspension with enhanced solubility, stability, and aerosolization performance for dry powder inhalation. Int J Pharm. 2017;533(1):84–92.

61. Bosquillon C, Lombry C, Preat V, Vanbever R. Influence of formulation excipients and physical characteristics of inhalation dry powders on their aerosolization performance. J Control Release. 2001;70:329–39.

62. Marek SR, Donovan MJ, Smyth HDC. Effects of mild processing pressures on the performance of dry powder inhaler formulations for inhalation therapy (1): Budesonide and lactose. Eur J Pharm Biopharm. 2011;78(1):97–106.

63. Lu P, Li J, Liu C, Yang J, Peng H, Xue Z, *et al*. Salvianolic acid B dry powder inhaler for the treatment of idiopathic pulmonary fibrosis. Asian J Pharm Sci. 2022;17(3):447–61.

64. Zhao Z, Zhang X, Cui Y, Huang Y, Huang Z, Wang G, *et al*. Hydroxypropyl-β-cyclodextrin as anti-hygroscopicity agent in amorphous lactose carriers for dry powder inhalers. Powder Technol. 2019;358:29–38.

65. Wang H, George G, Islam N. Nicotine-loaded chitosan nanoparticles for dry powder inhaler (DPI) formulations – Impact of nanoparticle surface charge on powder aerosolization. Adv Powder Technol. 2018;29(12):3079–86.

66. Zimmermann CM, Baldassi D, Chan K, Adams BP, Neumann A, Porras-Gonzalez DL, *et al*. Spray drying siRNA-lipid nanoparticles for dry powder pulmonary delivery. J Control Release. 2022;351:137–50.

67. Yu H, Teo J, Chew JW, Hadinoto K. Dry powder inhaler formulation of high-payload antibiotic nanoparticle complex intended for bronchiectasis therapy: Spray drying versus

spray freeze drying preparation. Int J Pharm. 2016;499(1–2):38–46.

68. Yu S, Pu X, Ahmed MU, Yu HH, Mutukuri TT, Li J, *et al*. Spray-freeze-dried inhalable composite microparticles containing nanoparticles of combinational drugs for potential treatment of lung infections caused by Pseudomonas aeruginosa. Int J Pharm. 2021;610:121248.

69. Lebhardt T, Roesler S, Uusitalo HP, Kissel T. Surfactant-free redispersible nanoparticles in fast-dissolving composite microcarriers for dry-powder inhalation. Eur J Pharm Biopharm. 2011;78(1):90–6.

70. Son YJ, Worth Longest P, Hindle M. Aerosolization characteristics of dry powder inhaler formulations for the excipient enhanced growth (EEG) application: Effect of spray drying process conditions on aerosol performance. Int J Pharm. 2013;443(1–2):137–45.

71. Wang H, George G, Bartlett S, Gao C, Islam N. Nicotine hydrogen tartrate loaded chitosan nanoparticles: Formulation, characterization and in vitro delivery from dry powder inhaler formulation. Eur J Pharm Biopharm. 2017;113:118–31.

72. Aquino RP, Prota L, Auriemma G, Santoro A, Mencherini T, Colombo G, *et al*. Dry powder inhalers of gentamicin and leucine: Formulation parameters, aerosol performance and in vitro toxicity on CuFi1 cells. Int J Pharm. 2012;426(1–2):100–7.

73. Mönckedieck M, Kamplade J, Fakner P, Urbanetz NA, Walzel P, Steckel H, *et al*. Dry powder inhaler performance of spray dried mannitol with tailored surface morphologies as carrier and salbutamol sulphate. Int J Pharm. 2017;524(1–2):351–63.

74. Ali ME, Lamprecht A. Spray freeze drying for dry powder inhalation of nanoparticles. Eur J Pharm Biopharm. 2014;87(3):510–7.

75. Suwandecha T, Wongpoowarak W, Maliwan K, Srichana T. Effect of turbulent kinetic energy on dry powder inhaler performance. Powder Technol. 2014;267:381–91.

76. Maloney SE, Alshiraihi IM, Singh A, Stewart IE, Mariner Gonzalez J, Gonzalez-Juarrero M, *et al*. Spray dried tigecycline dry powder aerosols for the treatment of nontuberculous mycobacterial pulmonary infections. Tuberculosis. 2023;139:102293.

77. Kunda NK, Alfagih IM, Miyaji EN, Figueiredo DB, Gonçalves VM, Ferreira DM, *et al*. Pulmonary dry powder vaccine of pneumococcal antigen loaded nanoparticles. Int J Pharm. 2015;495(2):903–12.

78. El-Gendy N, Pornputtapitak W, Berkland C. Nanoparticle agglomerates of fluticasone propionate in combination with albuterol sulfate as dry powder aerosols. Eur J Pharm Sci. 2011;44(4):522–33.

79. Jafarinejad S, Gilani K, Moazeni E, Ghazi-Khansari M, Najafabadi AR, Mohajel N. Development of chitosan-based nanoparticles for pulmonary delivery of itraconazole as dry powder formulation. Powder Technol. 2012;222:65–70.

80. Kinnunen H, Hebbink G, Peters H, Huck D, Makein L, Price R. Extrinsic lactose fines improve dry powder inhaler formulation performance of a cohesive batch of budesonide via agglomerate formation and consequential co-deposition. Int J Pharm. 2015 ;478(1):53–9.

81. Zhao H, Le Y, Liu H, Hu T, Shen Z, Yun J, *et al*. Preparation of microsized spherical aggregates of ultrafine ciprofloxacin particles for dry powder inhalation (DPI). Powder Technol. 2009;194(1–2):81–6.

82. Han CS, Kang JH, Park E-hye, Lee HJ, Jeong SJ, Kim DW, *et al*. Corrugated surface microparticles with chitosan and levofloxacin for improved aerodynamic performance. Asian J Pharm Sci. 2023;18(3):100846.

83. El-Gendy N, Huang S, Selvam P, Soni P, Berkland C. Development of budesonide nanocluster dry powder aerosols: Formulation and stability. J Pharm Sci. 2012;101(9):3445–55.

84. Faulhammer E, Wahl V, Zellnitz S, Khinast JG, Paudel A. Carrier-based dry powder

inhalation: Impact of carrier modification on capsule filling processability and in vitro aerodynamic performance. Int J Pharm. 2015;491(1–2):231–42.

85. Donovan MJ, Smyth HDC. Influence of size and surface roughness of large lactose carrier particles in dry powder inhaler formulations. Int J Pharm. 2010;402(1–2):1–9.

86. Balducci AG, Steckel H, Guarneri F, Rossi A, Colombo G, Sonvico F, *et al*. High shear mixing of lactose and salmeterol xinafoate dry powder blends: Biopharmaceutic and aerodynamic performances. J Drug Deliv Sci Technol. 2015;30:443–9.

87. Hassoun M, Ho S, Muddle J, Buttini F, Parry M, Hammond M, et al. Formulating powder-device combinations for salmeterol xinafoate dry powder inhalers. Int J Pharm. 2015;490(1–2):360–7.

88. Kadota K, Tanaka M, Nishiyama H, Tse JY, Uchiyama H, Shirakawa Y, *et al*. An effective approach to modify the inhalable betamethasone powders based on morphology and surface control using a biosurfactant. Powder Technol. 2020;376:517–26.

89. Ógáin ON, Li J, Tajber L, Corrigan OI, Healy AM. Particle engineering of materials for oral inhalation by dry powder inhalers. I - Particles of sugar excipients (trehalose and raffinose) for protein delivery. Int J Pharm. 2011;405(1–2):23–35.

90. Yazdi AK, Smyth HDC. Carrier-free high-dose dry powder inhaler formulation of ibuprofen: Physicochemical characterization and in vitro aerodynamic performance. Int J Pharm. 2016;511(1):403–14.

91. Lee HJ, Lee HG, Kwon YB, Kim JY, Rhee YS, Chon J, *et al*. The role of lactose carrier on the powder behavior and aerodynamic performance of bosentan microparticles for dry powder inhalation. Eur J Pharm Sci. 2018;117:279–89.

92. Lechanteur A, Plougonven E, Orozco L, Lumay G, Vandewalle N, Léonard A, *et al*. Engineered-inhaled particles: Influence of carbohydrates excipients nature on powder properties and behavior. Int J Pharm. 2022;613:121367.

93. Peng T, Lin S, Niu B, Wang X, Huang Y, Zhang X, *et al*. Influence of physical properties of carrier on the performance of dry powder inhalers. Acta Pharm Sin B. 2016;6(4):308–18.

94. Elia A, Cocchi M, Cottini C, Riolo D, Cafiero C, Bosi R, *et al*. Multivariate data analysis to assess dry powder inhalers performance from powder properties. Powder Technol. 2016 ;301:830–8.

95. Shetty N, Park H, Zemlyanov D, Mangal S, Bhujbal S, Zhou Q. Influence of excipients on physical and aerosolization stability of spray dried high-dose powder formulations for inhalation. Int J Pharm. 2018;544(1):222–34.

96. Hickey AJ, Martonen TB, Yang YY. Theoretical relationship of lung deposition to the fine particle fraction of inhalation aerosols. Pharm Acta Helv. 1996;7(1):185-90.

97. Yousuf Khan M, Qureshi M, Nazir T, -Ur-Rahman N, Khan M, Yousuf M. Effect of coating material on the aerodynamic particle size distribution (PSD) of Oxis Turbohaler® using mixing inlet with an Andersen cascade impactor (ACI). J Appl Pharm. 2011;2(3):165-178.

98. Alhajj N, Zakaria Z, Naharudin I, Ahsan F, Li W, Wong TW. Critical physicochemical attributes of chitosan nanoparticles admixed lactose- PEG 3000 microparticles in pulmonary inhalation. Asian J Pharm Sci. 2020;15(3):374–84.

99. Alhajj N, Naharudin I, Colombo P, Quarta E, Wong TW. Probing critical physical properties of lactose-polyethylene glycol microparticles in pulmonary delivery of chitosan nanoparticles. Pharmaceutics. 2021;13(10):1–10.

100. Wang YB, Watts AB, Peters JI, Liu S, Batra A, Williams RO. In vitro and in vivo performance of dry powder inhalation formulations: Comparison of particles prepared by thin film freezing and

micronization. AAPS PharmSciTech. 2014;15(4):981–93.

101. Mangal S, Park H, Zeng L, Yu HH, Lin YW, Velkov T, *et al*. Composite particle formulations of colistin and meropenem with improved in-vitro bacterial killing and aerosolization for inhalation. Int J Pharm. 2018;548(1):443–53.

102. Shiehzadeh F, Hadizadeh F, Mohammadpour A, Aryan E, Gholami L, Tafaghodi M. Streptomycin sulfate dry powder inhalers for the new tuberculosis treatment schedule. J Drug Deliv Sci Technol. 2019;52:957–67.

103. Lu P, Li J, Liu C, Yang J, Peng H, Xue Z, *et al*. Salvianolic acid B dry powder inhaler for the treatment of idiopathic pulmonary fibrosis. Asian J Pharm Sci. 2022;17(3):447–61.

104. Abiona O, Wyatt D, Koner J, Mohammed A. The optimisation of carrier selection in dry powder inhaler formulation and the role of surface energetics. Biomedicines. 2022;10(11):2707.

105. Mei B, Tan J, Liew CV, Chan LW, Wan P, Heng S, *et al*. Particle surface roughness-its characterisation and impact on dry powder inhaler performance. pulmonary drug delivery: Advances and challenges. Wiley; 2015;199-222.

106. Wang H, Nobes DS, Vehring R. Particle surface roughness improves colloidal stability of pressurized pharmaceutical suspensions. Pharm Res. 2019;36(3):1-7.

107. Scherließ R, Bock S, Bungert N, Neustock A, Valentin L. Particle engineering in dry powders for inhalation. Eur J Pharm Sci. 2022;172:1–10.

108. Lau M, Young PM, Traini D. Investigation into the manufacture and properties of inhalable high-dose dry powders produced by comilling API and lactose with magnesium stearate. AAPS PharmSciTech. 2017;18(6):2248–59.

109. Lechanteur A, Evrard B. Influence of composition and spray-drying process parameters on carrier-free DPI properties and behaviors in the lung: a review. Pharmaceutics. 2020;12(1):1–21.

110. Abruzzo A, Giordani B, Miti A, Vitali B, Zuccheri G, Cerchiara T, *et al*. Mucoadhesive and mucopenetrating chitosan nanoparticles for glycopeptide antibiotic administration. Int J Pharm. 2021;606.

111. Dong W, Ye J, Zhou J, Wang W, Wang H, Zheng X, *et al*. Comparative study of mucoadhesive and mucus-penetrative nanoparticles based on phospholipid complex to overcome the mucus barrier for inhaled delivery of baicalein. Acta Pharm Sin B. 2020 ;10(8):1576–85.