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Review Article

Spray Dried Nanoparticle for Pulmonary Delivery: Current Developments and Future Perspectives

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ABSTRACT

Aim: The study aims to comprehensively review advancements in spray-dried nanoparticles for pulmonary drug delivery. It focuses on understanding current techniques, nanoparticle types and applications. Additionally, it aims to identify challenges, assess developments critically and propose future perspectives. The research explores strategies to enhance nanoparticle efficiency, safety and targeted lung delivery. The ultimate goal is to provide valuable insights guiding researchers, pharmaceutical scientists and healthcare professionals in optimizing the design for improved therapeutic strategies in respiratory diseases, leading to better patient outcomes. **Background:** Dry Powder Inhalers (DPIs) have emerged as a popular method for delivering therapeutic aerosols to the lungs, targeting respiratory conditions including lung cancer, asthma, COPD, cystic fibrosis and pulmonary arterial hypertension. With their huge surface area for absorption, lower metabolic activity than other organs, many capillaries and thin air-blood barrier, the lungs will be significant advantages for systemic medication administration. The particle size shall play a significant role in their deposition in the respiratory tract. **Conclusion:** A promising formulation technique that combines the advantages of nanotherapeutics and the aerodynamics necessary for effective pulmonary medication administration is combined by controlled agglomeration of Nanoparticles (NPs) into micron-sized clusters. For the creation of microparticles from colloidal solutions containing NPs, spray drying is a flexible approach that is frequently used. The formulation and process characteristics of NP-based drug delivery systems, as well as improvements in spray drying technology. To promote their commercialization, future research should concentrate on scaling up the manufacturing of NP agglomerates and establishing downstream processing strategies.

Keywords: Dry powder inhaler, pulmonary drug delivery, spray drying, drug nanoparticle

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INTRODUCTION

Dry Powder Inhalers (DPIs) have emerged as a popular method for delivering therapeutic aerosols to the lungs, targeting respiratory conditions including lung cancer, asthma, COPD, cystic fibrosis and pulmonary arterial hypertension. With their huge surface area for absorption, lower metabolic activity than other organs, many capillaries and thin air-blood barrier, the lungs have significant advantages for systemic medication administration. To deliver drugs to the lungs, they must be presented as aerosols, which are colloidal dispersions of liquid droplets or solid particles suspended in gases with sufficient stability.[1] The particle size plays a significant part in their deposition within the respiratory tract. The particle size distribution of an aerosol is frequently expressed using the mass median aerodynamic diameter. Larger particles with a high mass median aerodynamic diameter deposit in the airway bifurcation through impaction when inhaled at high velocity, while smaller particles deposit deeper in the lungs through sedimentation and impaction. Breath-holding periods can enhance deposition by allowing more time for particles with lower settling velocity to settle. It is often believed that submicron particles, due to their low settling velocity, are exhaled.[2] However, despite the risk of exhalation, these particles can distribute throughout the lungs and reach the distal airways.[3] To deliver a dry powder formulation to the lungs for local or systemic pharmacological effects, special equipment known as Dry Powder Inhalers (DPIs) must be used.[4] These DPIs play a pivotal role in the effective administration of drugs in the form of dry powder to the lungs. Moreover, with the expected reduction in the use of hydrofluoroalkane propellants due to climate change concerns, the development and utilization of DPIs are anticipated to grow further (Figure 1).

Numerous reviews have been published, specifically addressing the deposition of particles within the lungs, the advancements in Dry Powder Inhalers (DPIs) and the formulation strategies employed for inhalable dry powders (Table 1).[5]

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Nanoparticle Engineering: Advancements in Formulations for DPIS

To achieve successful delivery of drugs to the lungs, drug particles must have an aerodynamic diameter smaller than 10 μm. To achieve topical delivery or targeted deposition in the small airways, a median aerodynamic diameter in the range of about 2 to 6 micrometers and 1 to 3 micrometers respectively, is desirable. Fine drug particles of such sizes have a high surface free energy, leading to increased cohesiveness and adhesivity of the powder. However, they often face challenges related to poor flowability and aerosolization performance, as they tend to be retained within the device when used alone. The prevailing method in Dry Powder Inhaler (DPI) formulations is to blend fine drug particles with an inert carrier, typically lactose, composed primarily of larger particles.[19,20] Fine drug particles stick to the surfaces of the carrier particles during blending, creating sticky combinations. There are three steps involved in the dispersion of medication particles from these sticky mixes during inhalation: (i) the separation of primary and agglomerated drug particles, the fluidization of the powder in the airstream and the breakdown of agglomerates into primary particles.[21] Particle engineering for pulmonary medication administration has developed over the past three decades, particularly in the development of carrier-free particles. These particles eliminate the challenges associated with carrier presence, such as blend uniformity and enable the delivery of high drug payloads to the lungs, which is particularly beneficial for antibiotics administration. However, it is important to note that carrier-free formulations may experience increased aggregation, potentially resulting in reduced emitted doses. Among carrier-free particles, spheroids (soft agglomerates of micronized particles) are widely recognized. They're employed in devices like the turbohaler (AstraZeneca), which, upon inhalation, breaks them down into separate particles. Spheroids typically measure 0.5 mm in diameter, exhibiting improved flowability compared to micronized particles and avoiding problems with electrostatic charging while handling and using.

Pulmonary drug delivery enhanced by nanoparticles

According to the US FDA, materials are categorized as nanoscale if they possess at least a size within the range of 1-100 nm. However, the ceiling of 100 nm is viewed as limiting. A broader definition encompasses particles measuring below 1000 nm in all dimensions. (sub-micron particles) within the category of nanoparticles (NPs).[22] In the pharmaceutical field, this latter definition is particularly relevant as the properties of materials and powders, processes like aggregation, dissolution and solubility exhibit notable alterations as particle size diminishes to the sub-micron scale. These changes are attributed to higher cohesiveness,[23] ratio of surface to volume,[24] and curvature.[25] The utilization of Nanoparticles (NPs) in drug delivery has grown considerable traction, with extensive research focused in recent years on NP-based medication delivery systems. NP-based formulations have grown to be among the most prominent strategies to address the issue of low solubility in drug development, consequently enhancing the bioavailability of medicines with limited water solubility. NPs give a higher surface area accessible for solvation due to their smaller particle size, which increases the pace at which solid medicines dissolve. Additionally, because of their greater particle curvature and the insertion of crystal lattice defects, Nanoparticles (NPs) might demonstrate improved solubility compared to microparticles.[26] We have conducted a comprehensive analysis on the impact of decreasing particle size on the dissolution rates, saturation solubility and *in vivo* performance of drug nanoparticles. When pharmaceuticals are formulated as NPs, a greater dose can be obtained than when they are dissolved in a solution, where the dose is constrained by the drug's solubility. Polymeric micelles, nanocomplexes, nano emulsions, virosomes, liposomes, polymeric nanoparticles and nanocrystals represent just a selection of the diverse range of nanotherapeutics employed in drug delivery (Figure 2).

Since the advantages associated with Nanoparticles (NPs) can also be applied to the pulmonary route of medication delivery. The percentage of the deposited drug that dissolves within the lung tissue determines the absorption and local bioavailability of pharmaceuticals administered to the lungs, as stated.[27] Low dissolution rate medications may be removed by mucociliary from the lungs before adequate absorption takes place, reducing local bioavailability. However, NP-based formulations have demonstrated the capacity to enhance absorption following the inhalation of medications with slow absorption resulting from poor water solubility, such as beclomethasone dipropionate and budesonide, due to dissolution constraints[28] When it comes to pulmonary drug delivery, NP-based therapeutics offer several advantages. They can achieve therapeutic effects in the lungs at lower doses compared to oral delivery, promote NP, enhance drug delivery of poorly water-soluble medicines, safeguard therapeutic agents against mucociliary clearance and protect medications from degradation internalization.[29]

Inhalable dry powders empowered by nanoparticles

The preparation of Nanoparticles (NPs) typically occurs in a liquid medium, creating a nanosuspension that behaves as a colloidal system. The physical instability problems that these liquid nanosuspensions are susceptible to include sedimentation, creaming, crystal development (also known as Ostwald ripening), aggregation and solid-state changeover.[30] Consequently, maintaining the nanosuspension's particle size becomes challenging during storage. On the contrary solid dose formulations provide better chemical and physical stability. To achieve optimal deposition in the lungs, it is important to consider two specific particle size ranges: 1 to 5 μm and 50 nm or less.[31] There is a considerable chance that NPs bigger than 50 nm will be exhaled before deposition when they are administered to the lungs.[32] Additionally, NPs in passive Dry Powder Inhalers

(DPIs) tend to significantly cluster during aerosolization at normal airflow rates and their cohesive nature makes handling particularly challenging.[33] Proposals have been made for the controlled clustering of nanoparticles into micron-sized clusters as a solution to circumvent these restrictions. This method combines the benefits of nanoparticles using the aerodynamics of tiny microparticles, enhancing the drug's bioavailability and aerosolization behaviour.[34] Therefore, solidifying nanosuspensions into inhalable NP agglomerates within the 1-5 μm size range can be a viable strategy for effectively administering NPs to the lungs using DPIs. Converting NPs into inhalation powders presents several challenges, NP agglomerates must be effectively redispersed in the lung fluid, particle size must be maintained in the dry state and the biological activity of therapeutic agents,

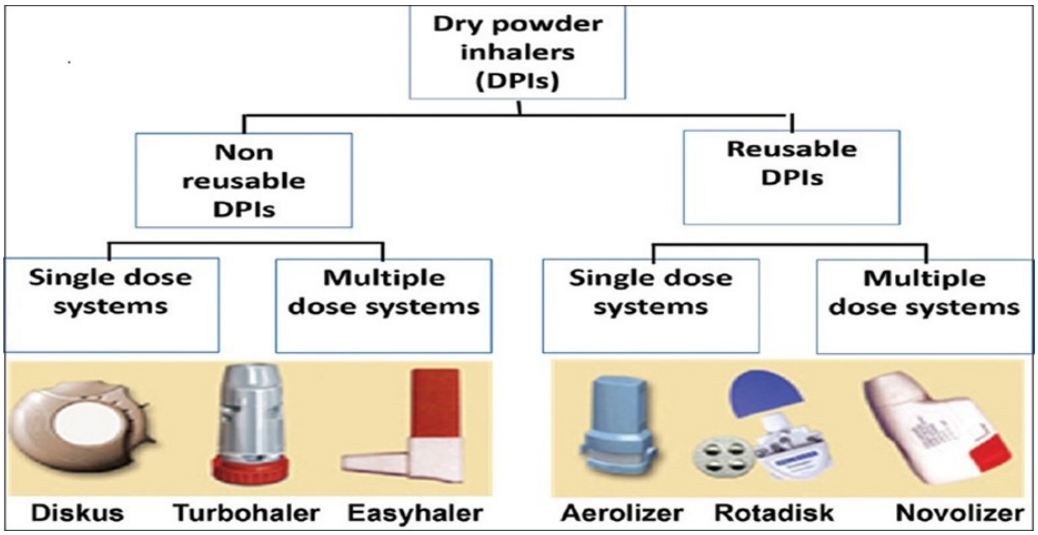

Figure 1: Types of Dry Powder Inhalers (DPIs). Reproduced, by permission, from reference.[5]

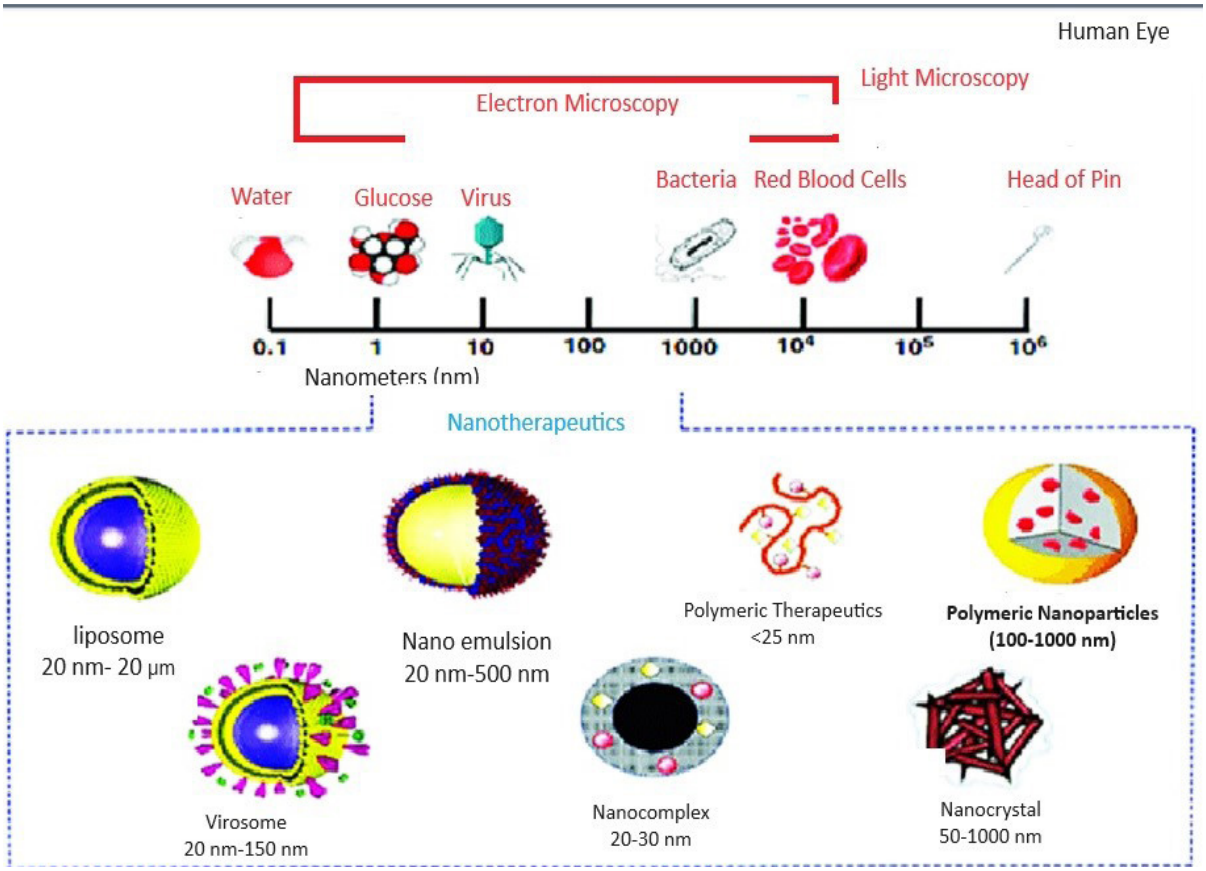

Figure 2: Nanoscale comparison and types of nanotherapeutics used in drug delivery system. Remodified, by permit, from reference.[27]

Table 1: Deposition of pulmonary particles, creation of dpis and formulation.

Author(s)	Reference	Topics Covered
Pulmonary particle deposition		
Chantal Darquenne (2012)	6	-Mechanisms influencing how inhaled aerosol is transported and deposited in the human lung. -The relationship between the medicinal effects of inhaled medicines and their pattern of deposition.
Andrew R. Martin *et al.* (2018)	7	- Relation between Lung and Systemic Exposure to Inhaled Drugs with Deposition and Pharmacokinetic Models within Time.
Cheng *et al.* (2018)	8	- *In vitro* measurements of airway flow and Experimental characterisation of the extrathoracic airway geometry - Inhaler and Drug Particle Characterization.
Liang *et al.* (2019)	9	- Pathological Mechanisms and Altered Barrier Function in Obstructive Lung Disease. -Anatomy and Functional Roles of Lung Barrier Systems in Different Pulmonary Regions.
Advancements in Dry Powder Inhaler (DPI) Technology		
Islam *et al.* (2012)	10	-Essential Mechanisms of Drug Delivery from Dry Powder Inhalers (DPIs) . -DPIs for systemic delivery. -Key factors which motivate and constrain of DPIs. - Performance of existing and under development devices.
Hagedoorn *et al.* (2014)	11	- Strategies for Particle Engineering. - Misconceptions about optimal DPI. use (e.g., pressure drop, device resistance). -Computational fluid dynamics.
de Boer *et al.* (2017)	12	-Advancements in Systemic Drug and Vaccine Delivery via Dry Powder Inhalers (DPIs). -Design DPIs and pulmonary drug deposition and distribution.
Rekkas *et al.* (2018)	13	-Utilizing Quality by Design in the Research Field: Practical Application.
Izquierdo Alonso *et al.* (2019)	14	-Understanding the Operational Principles and Essential Features of DPIs for Tailored Patient Prescription.
Formulations for DPIs		
Al-Hallak *et al.* (2011)	15	-Exploring Therapeutic and Diagnostic Applications of Inhalable Nanoparticles as Dry Powder Inhalers (DPIs) in Animal Models: *In vivo* Findings. -Enhancing Deep Lung Deposition and Redispersibility of Nanoparticles (NPs) as Dry Powder Inhalers (DPIs): Formulation Strategies.
Tajber *et al.* (2014)	16	-Advancements in Powder Formulation and Inhaler Design for Carrier-Free Dry Powder Inhalers (DPIs): Various Approaches.
Smyth *et al.* (2018)	17	-Overcoming Barriers in High-Dose Pulmonary Delivery: Formulation Techniques (such as Hollow Particles and Particle Surface Modification).
Lakerveld *et al.* (2018)	18	-Particle Engineering Techniques for Drug Manufacturing in Dry Powder Inhalers (DPIs): Direct Control Crystallization, Spray Drying, Freeze Drying and Micronization.

particularly biotherapeutics, must be preserved throughout the processing steps.[35] Entrapping the NPs in a matrix of excipients, such as water-soluble sugar-based compounds, is one method of overcoming these difficulties. Using this technique, micron-sized particles made up of NPs embedded in matrix formers can be created. Until they reach the pulmonary mucus lining, where the highly soluble matrix formers breakdown and release the NPs, these composite particles function as an intermediary delivery method.[36,37] There are other particle engineering methods that have been developed, such as spray drying, freeze drying, spray-freeze drying and aerosol flow reactor.

Spray Drying for Enhanced Particle Engineering

Using spray drying is a tried-and-true method that has found extensive application across diverse domains, including both the chemical and food industries. When it first emerged in the early 20th century, the pharmaceutical business was initially employed for sanitizing blood. Over time, spray drying has found diverse applications in pharmaceuticals, such as the drying of biopharmaceuticals, the creation of amorphous solid dispersions and the encapsulation of medications and essential oils in excipient matrices like proteins, vaccines, DNA and antibodies.[38,39] In the

pharmaceutical realm, spray drying is extensively utilized to produce powders with particle sizes ranging from the nanometer to the micrometer scale. This technique offers great control and manipulation over various powder properties, comprising crystallinity, dispersibility, flowability, moisture content and particle size dispersion.[40] Moreover, spray drying serves as a versatile platform both for crystal engineering and particle engineering. The spray drying process involves a manufacturing procedure in which the process involves converting a liquid feed into a dry particle form in a single step. The core principle of the method workings center on the conversion of the liquid input into minuscule droplets through atomization followed by the solvent evaporating through interaction with a heated drying gas. In the foundational steps of this process for liquid feedstock preparation, four key stages emerge: first, the feed is atomized into a spray via a nozzle, then it engages with the hot drying gas. Next, particles form as the liquid transfers from droplets into the drying gas through evaporative mass transfer. Finally, the dried product is separated from the gas, culminating in these vital four steps (Figure 3).[41]

Liquid feed pump preparation

The liquid feed used in spray drying must possess a viscosity that allows for easy pumping. This feed solution can be prepared from a suspension or emulsion comprising the active substance, excipients, solvents, or a combination of solvents. The selection of the qualitative and quantitative composition of the feed pump considers the desired characteristics of the target product as well as the solubility requirements of the active substances

Spray Drying Process Parameter

The inlet temperature

The inlet temperature of the drying gas that is heated immediately prior to entering the chamber for the drying process. The thermal energy carried by the incoming drying gas influences its efficiency in drying atomized droplets. Higher inlet temperatures lead to accelerated solvent evaporation rates. However, it's crucial to emphasize that merely raising the inlet temperature may not consistently result in enhanced drying efficiency, as it can also influence the wet-bulb temperature of the surrounding air. Low inlet temperatures, on the other hand, result in lower surrounding air wet-bulb temperatures, thereby reducing the risk of thermal degradation of the final product. Consequently, selecting the optimal inlet temperature requires careful consideration of these factors, considering the properties of the feedstock.[42,43]

Outlet temperature

The temperature of the air, which holds the dehydrated particles just before entering the collection devices, is denoted as the output temperature. In counter-current dryers, even though the final product may possess a higher temperature compared to the output air, the outlet temperature theoretically represents the maximum temperature attainable by the dehydrated powder. The outlet temperature is determined by various transfers of mass and heat that occur within the drying area, but not immediately controlled by the operator. Instead, it is influenced by parameters such as the inlet temperature, the flow rate of the drying gas and the properties of the feed, including the enthalpy of solvent evaporation and the concentration of solid particles in the droplets.[42,43]

Aspirator speed

A higher aspiration speed (55%) results in a shorter residence time in the drying devices, which leads to increased moisture content and a higher degree of separation into cyclones. On the other hand, a lower aspiration speed (25%) causes over-drying of the product, with most of the material being retained in the drying chamber. As a result, an aspiration speed of 40-50% was chosen for further studies to strike a balance between residence time and moisture content, achieving optimal drying outcomes.

Feed pump

At a controlled rate, the feedstock solution is poured into the atomizer, while maintaining a constant atomization pressure. When it comes to emulsions and suspensions, the liquid feed's stability is crucial, as it affects both the spray-dried product's uniformity and the potential for operational nozzle blockage in the dryer. To ensure efficient spray drying of colloidal systems, it is important to prevent clogging, ensure that the size of the dispersed phase is smaller than the nozzle orifice. It has been observed that an increase in higher solids concentration in the liquid feed can lead to the formation of larger particles and an increased effective particle density.[43,44]

Atomization

During this step the liquid feed is transformed into the droplets using a nozzle. Different types of atomizers are available for spray dryers, both for development purposes and commercial pharmaceutical applications. In the pharmaceutical sector, two-fluid nozzles are frequently employed to create respirable particles, ability to accommodate smaller-scale plants and their ability to generate smaller droplet sizes compared to other atomizers. Atomization happens as the supplied gas rapidly expands, mixing either internally or externally with the liquid feed depending on the nozzle type. At the nozzle opening, the gas velocity greatly surpasses that of the liquid, which is crucial for generating a substantial spray surface. A detailed examination was conducted on the production of inhalable particles using both spray drying and atomization with a two-fluid nozzle.[45]

Rotary atomizers

The feedstock solution is directed towards the center of a horizontal wheel or disc, which is how rotary atomizers are

constructed. Then centrifugal force is used, accelerating feeding solution to the edge, where it condenses as a shower of droplets. The design of atomizer discs allows for better management of solution dispersion due to rapid velocity generated by the rotation.[42,43]

Hydraulic nozzle atomizers

Also referred to as one-fluid nozzles, hydraulic nozzle atomizers function by pressurizing the solution and passing it through an outlet with a gradually reducing diameter. A tiny, high-velocity nozzle aperture, typically between 0.4 and 4 mm in diameter, releases the fluid. causing the pressure to drop sequentially This process leads to atomization, breaking the feed solution into droplets.[42,43]

Pneumatic nozzle atomizers

Pneumatic nozzles, also referred to as multi-fluid nozzles, often utilize a two-fluid configuration. These atomizers involve feeding the nozzle with two phases: the feedstock solution and an atomizing medium for compressed gas. The gas and liquid phases flow separately and meet inside the nozzle or none. The elevated gas velocity creates notable frictional forces on the liquid surface. Leading to atomization and the formation of a cloud of droplets. Weber has described this process, highlighting the influence of feed properties, gas velocity, density, direction and the liquid-to-gas ratio on atomization.[42,46]

Vacuum

As the aspirator speed increases, the vacuum level also increases. A higher vacuum level results in a shorter residence time of particles in the collector, which can directly impact the production yield. Therefore, vacuum levels ranging from -90 to -120 mmWc were tested to determine the optimal conditions.

Conversion from droplet to particle

Following atomization, during spray drying process advances into the important period of particle production characterized by two significant events: the interaction between the spray and the surrounding air and the subsequent drying of the droplets. These events collectively lead to the extraction of the solvent from the droplets, resulting in their conversion into dried particles.[47,48]

Drying

The removal of solvent from the droplets, known as the drying process, involves a combined transfer of heat and mass. It relies on the difference in vapor pressure between the solvent the gas phase of the droplet and its partial pressure as the driving force. There are two stages to the drying kinetics of droplets with suspended particles, such as nanoparticles. At the onset, during the constant-rate period, the distinctive feature is the evaporation of solvent from the droplet's surface, resulting in a consistent reduction in diameter. The second stage, known as the falling-rate period, commences on reaching the necessary moisture content. At this point, the solvent within the droplet interior becomes insufficient to maintain saturation across the entire surface, leading to the development of a shell through the particles aggregating at the liquid-air contact. Evaporation persists from the pores of the shell throughout this phase until reaching the equilibrium moisture content, signifying the conclusion of the drying process (Figure 4).[49,50]

The Peclet number (Pe) and the initial excipient saturation are two dimensionless metrics that can be used to describe particle formation during spray drying. According to Equation (1),[51] the Pe stands for the ratio of the liquid evaporation from the drying droplet equates to the diffusion rate of the dispersed phase toward the center of the droplet.

$$Pe=R^2/(\tau d\ D) \quad (1)$$

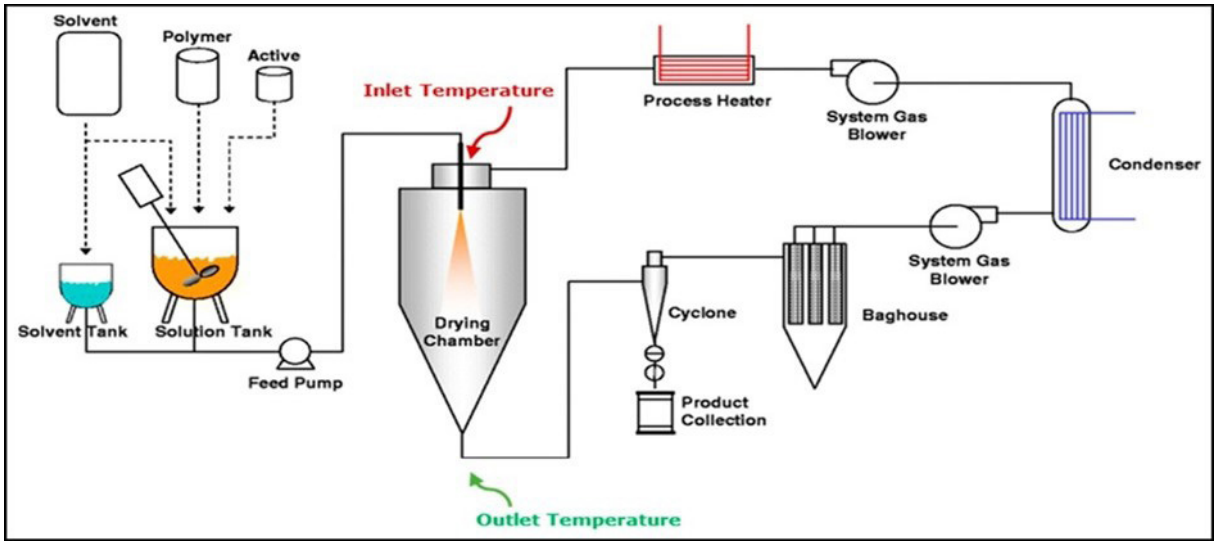

Figure 3: Schematic instrumentation for a spray dryer. permission, from reference.[90]

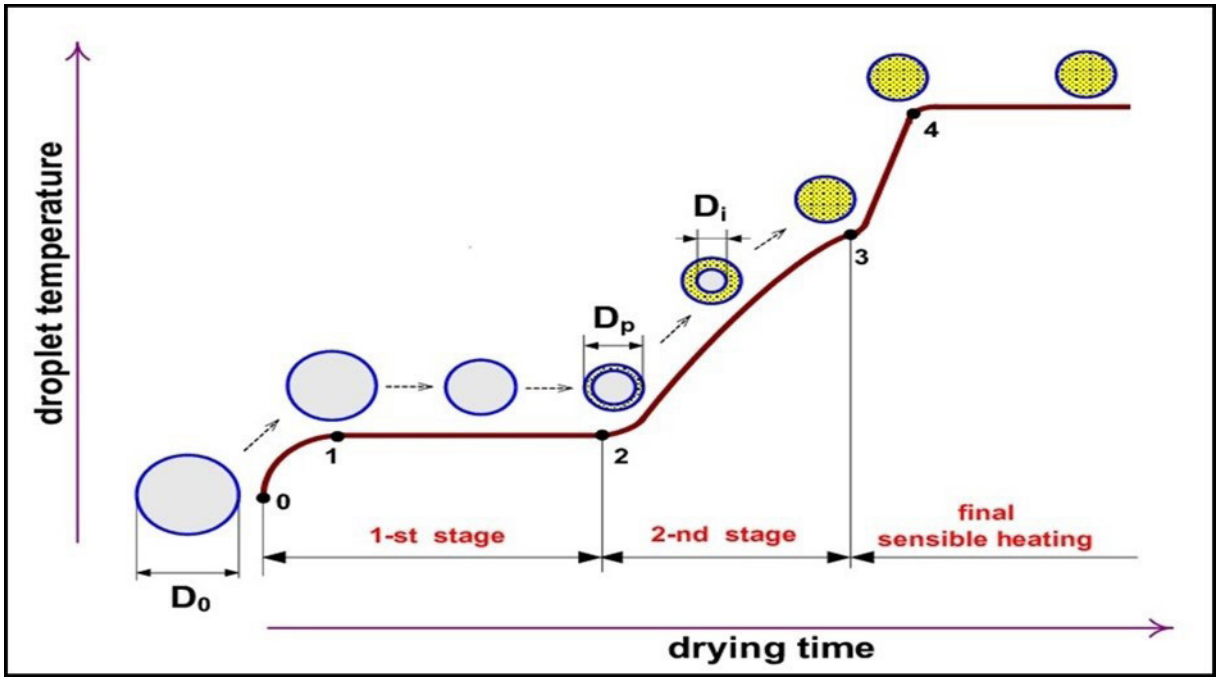

Figure 4: Drying kinetics of droplet temperature, with permission from reference.[49]

In this case, R stands for the droplet radius, D for the solute or nanoparticle diffusion coefficient and d for the droplet drying time. A high Pe value denotes both shrinking and the buildup of the dispersed phase at the surface. Equation (1) predicts that Pe will be governed by drying circumstances including temperature and solvent type, which have an impact on evaporation and drying time, as well as particle size and solubility of the dispersed phase, which have an impact on diffusivity. Particle diffusion is quicker or referring to the outward velocity of the retracting droplet surface for low Pe values (Pe 1). As a result, during evaporation, the particles stay evenly dispersed within the droplet, resulting in spherical particle agglomerates. On the other hand, with high Pe numbers (Pe>>1), there is not enough time for the particles to disperse and they end up accumulating where liquid and air meet. Hollow or doughnut-shaped particles are created as evaporation moves through the crust.[40,52] Additionally, during the last stages of drying, a flexible surface skin develops because of the viscoelastic behavior of materials, resulting in localised collapse and surface voids.[53] It has been found that the initial droplet volume, size and concentration of suspended particles all influence the morphology of spray-dried particles. Nanoparticle-containing suspensions have low Pe values because of a faster rate of diffusion. They become spherical aggregates or grains after drying, forming an irregularly shaped shell around a sphere.[50]

Separation

The process's last phase is the removal of the dried substances from the drying gas. Cyclones are frequently utilized for recovering finer particles, Although the primary division of dehydrated particles from the drying gas stream occurs close to the bottom of the drying area. Particles in a cyclone are subjected to centrifugal forces, which cause them to accumulate at the vessel's bottom. Spray-dried particles smaller than 2 μm can only be collected with a limited amount of efficiency by standard cyclones. They also suffer from poor efficiency in collecting fine particles, causing material loss in other spray dryer components, such as adherence to drying chamber walls, resulting in low production yield. This can be particularly disadvantageous for the spray drying of high-value biopharmaceuticals as it increases production costs.[54] The design and dimensions of the cyclone influence product recovery. Improvements in cyclone utilization have been found to enhance collection efficiency and a narrower cyclone design has been shown to increase the production yield of spray-dried amorphous products.[55] When producing inhalable particles through performing spray drying utilizing the Buchi B-290 equipped with the standard cyclone with product recovery of approximately 13% was achieved, whereas the use of a high-efficiency cyclone resulted in typical product yields of 50-70%.[56]

This passage discusses the manufacturing and therapeutic uses of different types of dry powder formulations based on Nanoparticles (NPs) produced using both traditional and non-conventional spray drying methods (Figure 5).

Study on Inhalable Spray-Dried Formulations Based on Nanoparticle

Microparticles containing nanopores

Nanoporous Microparticles (NPMPs) propose a particle engineering approach to improve lung deposition in inhalation treatments. These particles, characterized by large size, low mass

density and aerodynamic diameters between 1 to 3 μm, have shown improved aerosolization performance in comparison to non-penetrable particles, mainly because of their diminished propensity to aggregate.[57] The utilization of spray drying for the production of excipient-free NPMPs has been investigated.[58] A spray drying procedure is used to remove a solute (excipient, medication, or both) from a solvent-antisolvent mixture. The substance ammonium carbonate employed as a pore-forming agent to facilitate the formation of inhalable NPMPs.[59] Studies have examined the use of spray drying to produce NPMPs for inhalation with raffinose and trehalose.[60] Amorphous NPMPs with high glass transition temperatures (124°C for trehalose and 120°C for raffinose) were produced by spray drying from an 80:20 (v/v) methanol and n-butyl acetate mixed solvent. These NPMPs exhibited demonstrated robust physical stability at ambient conditions and exhibited promise as carriers and stabilizing agents for proteins. The successful integration of the model protein lysozyme into the NPMPs was achieved at a weight ratio of sugar to protein of 1:4, highlighting their potential for pulmonary delivery of peptides and proteins. The manufacture of NPMPs comprising trypsin with excipients like trehalose, raffinose and hydroxypropyl-cyclodextrin required the addition of water. The biological activity of trypsin was preserved and the NPMPs demonstrated fine particle fractions (FPFs) of approximately 45%, remaining stable under low relative humidity conditions at 4°C or 25°C.

The features of trehalose and raffinose powders intended for use as biomolecule carriers for inhalation were studied in relation to the effects of operating settings of a Buchi Mini Spray Dryer B-290.[61] Solutions of 80:20 (v/v) methanol n-butyl acetate were used for spray drying. The most important element influencing production yield, particle size and specific surface area was found to be gas flow. Due to their greater surface area, raffinose NPMPs showed higher FPFs during *in vitro* aerosolization tests than trehalose NPMPs. Therefore, raffinose NPMPs were considered the preferred dry powder formulation for inhalation. With promising aerodynamic and pharmacokinetic features seen for the transport of the therapeutic peptide salmon calcitonin, raffinose's usefulness as a non-reducing sugar for the creation of NPMPs containing biomolecules was also established.[62] The idea of NPMPs has been used to create inhalable dry powders of small molecular weight pharmaceuticals in addition to biomolecules. For instance, the feasibility of producing NPMPs of the hydrophilic drug sodium cromoglycate, commonly used in asthma treatment, was investigated by modifying a spray drying process originally developed for hydrophobic drugs.[63] The produced NPMPs exhibited enhanced *in vitro* drug deposition compared to the marketed product, showing improved aerosolization performance when tested through an Andersen Cascade Impactor (ACI) using the Spin haler-R device. Storage conditions influenced particle morphology and deposition performance, with NPMPs retaining their properties under dry conditions.

Ammonium carbonate, as a pore-forming agent, was explored for its impact on the characteristics of the anti-tubercular agent p-amino salicylic acid and its ammonium salt when spray dried from ethanol/water solvent systems.[64] The resulting nano-structured microparticles demonstrated potential for pulmonary delivery, exhibiting higher emitted doses in *in vitro* deposition studies using a Twin-Stage Impinger (TSI) compared to the micronized drug. Ammonium carbonate interacted with p-amino salicylic acid under suitable processing conditions, leading to the formation of a novel solid-state form. To address issues related to viscous mucus encountered in respiratory diseases and to improve budesonide diffusion within lung fluid, a combinatory NPMPs system of budesonide and the mucolytic drug ambroxol hydrochloride was developed for inhalation as a dry powder.[65] The ammonium carbonate-added co-spray-dried particles had better aerodynamic properties because it neutralised the ambroxol hydrochloride and produced ambroxol base as a result. This approach demonstrated promising aerosolization budesonide's effectiveness and increased permeability over mucus in a test tube, suggesting the potential of combined NPMPs with mucolytic agents for drug distribution, including antibiotics, to the lungs, particularly in diseases associated with abnormally

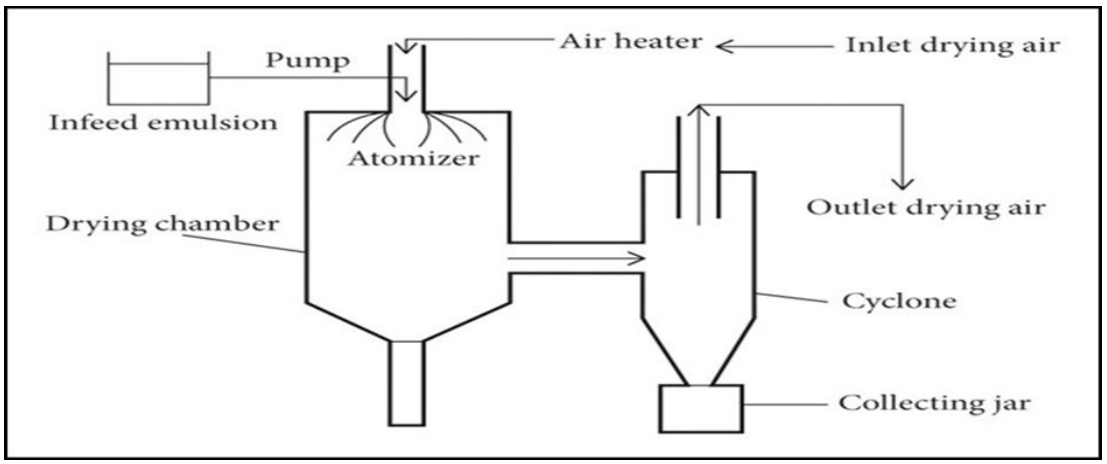

Figure 5: Cyclone separator.

viscous mucus (e.g., cystic fibrosis). In conclusion, spray drying to create NPMPs with non-reducing sugars and pore-forming ammonium carbonate forming is a practical particle engineering technique for creating dry powders that may be inhaled that include both biomolecules and small-molecule medications.

Nanocrystalline Accumulations

The benefits of both Nanoparticles (NPs) and the aerodynamics of microparticles are combined when NPs and microparticles are combined through controlled agglomeration. This section focuses on the spray drying process used to solidify medication nanocrystals into inhalable micron-sized particles composites known as nanocrystalline agglomerates. Various drugs have been successfully transformed into inhalable nanocrystalline agglomerates using nanosuspensions produced using top-down techniques (like wet milling and high-pressure homogenization) or bottom-up approaches (such as solvent/antisolvent precipitation), followed by spray drying.[66] Studies have shown that these nanocrystalline agglomerates exhibit improved dissolution profiles, facilitating their dissolution in the lungs.[67] To enhance the redispersibility and aerosolization performance of nanocrystalline agglomerates, excipients like mannitol and leucine have been incorporated into the nanosuspensions prior to spray drying.[68] The inclusion of these excipients has demonstrated improved enhanced drug dissolution, increased redispersibility after hydration and considerably enhanced *in vitro* aerosolization of the nanocrystalline agglomerates.[69] In a subsequent study using a low melting point applied experimental design, Ratios of leucine to drug and mannitol to drug, as well as the kind of stabiliser, were discovered to have a substantial impact on the process' total yield. The mannitol to drug ratio was found to be a crucial factor affecting redispersibility, whereas the aerosolization performance of the nanocrystalline agglomerates,[70] was affected by both the mannitol to drug ratio and the leucine to drug ratio.[72] These findings are in line with research which demonstrated the necessity of using water-soluble excipients like mannitol to enable the release of poly (lactic-co-glycolic acid) NPs from microparticles under simulated lung conditions.[53] Scanning electron microscopy images have shown the differences in morphology between nanocrystalline agglomerates of indomethacin with and without matrix formers, prepared using different stabilizer.[69] Another study developed inhalable nanocrystalline Tadalafil agglomerates within a dry powder formulation for addressing pulmonary arterial hypertension. D-optimal experimental design was employed to optimize formulation parameters, including the nanocrystal to L-isoleucine to sugar ratio, sugar kind and sugar ratio. In comparison to traditional oral administration, the study showed that pulmonary administration of tadalafil as nanocrystalline agglomerates resulted in a quicker onset of action, a greater local drug concentration and a longer drug retention in the lungs.[71]

The use of water-soluble medications and pharmacological combinations has been expanded to include nanocrystalline agglomerates.[72] Theophylline served as an example of how milling mannitol in an organic solvent while wet, then subsequently undergoing spray drying can be employed to produce respirable particles of water-soluble medicines or pharmaceuticals susceptible to crystal transformation. A comparison between two-fluid and three-fluid spray drying nozzles revealed that agglomerates obtained using a two-fluid nozzle from a nanosuspension of budesonide and mannitol exhibited superior production yield, homogeneity of drug content and aerodynamic performance compared to amorphous solid dispersion dry powders prepared using a three-fluid nozzle.[73] The two-fluid nozzle performed better than the three-fluid nozzle in terms of physical stability, crystallinity, dissolution and co-deposition profile while creating inhalable combination particles of budesonide and theophylline.[74] This research show how spray drying can be used widely to create nanocrystalline agglomerates of different medications for pulmonary delivery of therapeutic agents with local or systemic effects. This method's adaptability comes from its capacity to fine-tune a number of procedures (like nozzle type) and formulation factors (like stabilisers or matrix formers), making it appropriate for pharmaceuticals with a variety of physicochemical properties.

Polymeric Nanoparticles

The submicron solid colloidal particles known as polymeric Nanoparticles (NPs) are made of polymers that come from natural, artificial, or semi-artificial sources. Small molecular weight medicines and biomolecules are transported by these NPs. NPs can be enclosed in polymer-based carriers depending on the preparation process, loaded onto the polymer surface, or dispersed within the polymeric matrix. The commonly employed polymers for polymeric NP formation include Polylactic co-Glycolic Acid (PLGA), Polyethylene Glycol (PEG), alginate, gelatine and chitosan. leveraging the polymers' reduced toxic potential and biodegradable nature for pulmonary drug delivery.[75,76] In one study, created polymeric NPs of the anti-tubercular medication rifampicin that are available as dry powders.[77] A mixture of acetone and methanol was used to dissolve rifampicin and PLGA while solution of mannitol in water was prepared. Utilizing a nozzle with four fluid outlets, the solutions were spray dried, producing mannitol microspheres containing rifampicin/PLGA NP. *In vitro* aerosol performance testing demonstrated favorable Fine Particle Fraction (FPF) around 30%. Furthermore, it was discovered that the rifampicin/PLGA mannitol microspheres had higher *in vivo* absorption by macrophages in the alveoli of rate lungs than microspheres lacking mannitol. It created nanocomposite microparticles as inhalable dry powders to address problems with the immunosuppressant tacrolimus's poor solubility, instability, irregular bioavailability and adverse effects in the treatment of pulmonary arterial hypertension.[78] Through the emulsion solvent

evaporation process, tacrolimus was enclosed in acetalated dextran to produce polymeric NPs that were about 200 nm in size. In the presence of mannitol, these NPs were spray dried, resulting in NP agglomerates with raisin-like shapes and average geometric diameters of about 2 nm. *In vitro* aerosolization testing exhibited an FPF of 81.0% and a Median Aerodynamic Diameter (MMAD) of 3.57±0.57 μm has been achieved, allowing for deposition in the deep regions of the respiratory tract. The NP agglomerates showed no significant cytotoxic effect on A549 human adenocarcinoma alveolar epithelial cells, indicating their non-toxic nature. This study and subsequent investigations by the same research group suggested that acetalated dextran-based NP agglomerates hold promise for pulmonary drug delivery.[79,80]

(Rezazadeh M. *et al*) created mixed polymeric micelles with molecular weights of 1000 and 5000 Da based-on tocopherol succinate polyethylene glycol and added the chemotherapy drug paclitaxel to them.[81] For the purpose of creating dry powders for inhalation, these improved micelles were spray-dried with lactose. Only 30% of the medicine from different formulations was released within the first 72 hr., which is a slow drug release rate. When tested against the A549 cell line *in vitro*, the drug-loaded nano micelles exhibited higher cytotoxic activity compared to the free drug. When the drug nano micelles were spray-dried with lactose, the result obtained was a yield Fine Particle Fraction (FPF) of 60%, as determined by *in vitro* deposition tests using the ACI. These results show the potential of the paclitaxel nano micelles containing microparticles as a formulation for the treatment of lung cancer. To increase the antibacterial properties of ciprofloxacin and prolong its residence time in the lungs, also created NP agglomerates made of nano micelles using spray drying. They were able to successfully generate NP agglomerates with a median diameter of 1.7 m and an FPF of 60% by optimizing the procedure using a design of experiments methodology. Mannitol was used as the matrix forming and L-phenylalanine as the anti-adhesion agent to achieve this. Ciprofloxacin considerably improved the antibacterial effects it had on bacteria like Pseudomonas aeruginosa, Klebsiella pneumoniae and Streptococcus pneumoniae.[82] As a result, this technique shows potential for creating polymeric nano micelle-based optimized dry powder formulations for inhalation that can be used to treat pulmonary infections. Overall, the findings of these investigations demonstrate the wide range of polymers that are readily available, along with different preparation techniques and spray drying as a solidification phase, that can produce respirable NP agglomerates with improved efficacy and regulated drug release.

Advanced Spray-Drying Methods

Nano Spray Drying

The Traditional spray dryers have limited efficiency in collecting particles below 2 μm, making them unsuitable for producing Nanoparticles (NPs). In 2009, Buchi introduced the B-90 nano spray dryer as a substitute model specifically designed for NP production. Three essential components are included in this dryer: an electrostatic particle collector, gentle laminar drying flow and vibrating mesh spray technology. When compared to traditional spray dryers, these developments increase sample recovery by up to 90%.[83] The fundamentals and uses of the Nano Spray Dryer for pharmaceutical encapsulation have been thoroughly reviewed.[84] In example, employing a smaller mesh aperture size (4.0 m) and very diluted input solutions (0.1% w/w), nano spray drying is an effective technique for producing NPs.[85] Its use in the creation of dry powders based on NP intended for inhalation has been documented. In order to examine the creation of respirable protein powders containing trehalose (a stabiliser) using the Nano Spray Dryer B-90, They evaluated the effects of process performance and particle quality parameters on inlet temperature, ethanol and spray cap size content in the spray solution. The size of the spray cap had an impact on the effect of the inlet temperature on enzyme activity. improved ethanol percentage, smaller cap diameters and lower intake temperatures all contributed to improved product recovery. When the protein was spray dried without the use of ethanol and with a larger spray cap, it showed increased storage stability.[86] The Nano Spray Dryer utilized B-90 to produce inhalable powders of the anti-tubercular agent capreomycin sulphate.[87] The process parameters, such as membrane pore size, inlet temperature and solution concentration, were optimized using an experimental design methodology. When tested using the TSI (time-of-flight), the optimized capreomycin particles mixed with lactose showed about 27% respirable percentage. These promising results led to the integration of spray-dried capreomycin sulphate formulations in clinical trials targeting the treatment of multi-drug resistant tuberculosis. Moreover, research utilizing nano spray drying techniques has demonstrated that L-leucine can enhance the efficiency of dry powder aerosolization for delivering pulmonary medications.[88,89]

CONCLUSION

A promising formulation technique that combines the advantages of nanotherapeutics and the aerodynamics necessary for effective pulmonary medication administration is combined by controlled agglomeration of Nanoparticles (NPs) into micron-sized clusters. For the creation of microparticles from colloidal solutions containing NPs, spray drying is a flexible approach that is frequently used. The formulation and process characteristics of NP-based drug delivery systems, as well as improvements in spray drying technology, the research formulation of the medicine as a dry powder for inhalation has several benefits, including tailored distribution to the respiratory tract, altered release profiles, improved solubility of weakly water-soluble pharmaceuticals and increased efficacy and safety. To promote their commercialization, future research should concentrate on

scaling up the manufacturing of NP agglomerates and establishing downstream processing strategies.

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CONFLICTING OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DPIs: Dry powder inhalers, **COPD:** Chronic Obstructive Pulmonary Disease, **US FDA:** United States Food and Drug Administration, **NPs:** Nanoparticles, **Pe:** Peclet Number, **NPMPs:** Nanoporous Microparticles, **FPFs:** Fine Particle Fractions, **ACI:** Andersen Cascade Impactor, **TSI:** Twin-Stage Impinger, **µm:** micro meter, **DNA:** Deoxyribonucleic Acid, **PLGA:** Polylactic Co-Glycolic Acid, **PEG:** Polyethylene Glycol, **MMAD:** Median Aerodynamic Diameter, **MMWC:** MilliMeters per Water Column.

SUMMARY

Presents a comprehensive examination of the latest advancements in the kingdom of pulmonary drug delivery using spray-dried nanoparticles. The paper systematically explores the various techniques employed in the spray-drying process, the types of nanoparticles utilized and their specific applications in pulmonary delivery. Emphasizing a critical assessment, the review identifies challenges and limitations inherent in current methodologies and formulations.

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