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An overview of dry powder inhaler production methods

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ABSTRACT: In comparison with alternative delivery strategies, pulmonary administration of drugs may provide several benefits, especially when utilizing dry powder formulations. The studies have frequently concentrated on dry powder inhalers (DPIs) due to certain pros with regard to stability, dose, and patient preference. Milling, freeze-drying, spray-drying, and electrospray are the production methods for DPIs. Conventional carrier-based DPIs and new-generation carrier-free DPIs are two essential kinds of DPI formulations. In the marketplace today, carrier-based formulations generate the majority of DPIs. To improve the dispersibility of inhalable dry powders, formulation approaches typically involve the incorporation of micronized active pharmaceutical ingredients (APIs) with larger-sized particles, like lactose, as carriers. Nevertheless, in carrier-based formulations, the dose of drugs that could be given to patients is lower compared to carrier-free formulations. The lung deposition of the majority of carrier-based formulations is still not particularly high. Individuals who have a diagnosed allergy to lactose ought to avoid DPI products based on lactose carriers. Lactose can also interact with the functional groups of drugs or proteins since it is a reducing sugar. Furthermore, the quality and source of the lactose have been found to have a significant impact on a powder formulation's effectiveness. Carrier-free formulations seem like an advantageous choice in these situations. In this review, the formulation excipients of carrier-based and carrier-free DPIs were evaluated. Alternative delivery systems and production technologies for DPIs were also discussed.

KEYWORDS: Carrier; dry powder; excipient; inhalation.

1. INTRODUCTION

Delivery of medications via the pulmonary system represents a promising, noninvasive administration strategy [1]. The lungs' distinctive geometry, which includes their enormous area of surface, a thinner epithelial surface, a substantial level of blood circulation, as well as prevention of the first-pass effect, provides this [2]. Benefits of pulmonary administration include a capacity to deliver low dosages, a reduced risk of systemic side effects, and, for certain medications, a quick onset of action [3].

Unfortunately, there are some challenges related to pulmonary drug delivery that need to be focused on [4]. The respiratory passage's advanced defense mechanism against foreign particles perceives the delivered drugs as foreign and works to either eliminate them or deactivate them if deposited in the lungs. The patients' failure to utilize inhaler devices correctly and comply with the recommended dosage schedule is an additional problem [5].

There are three main categories of inhaled drug delivery devices: pressurized metered-dose inhalers (pMDIs), DPIs, and nebulizers [6]. There are advantages and disadvantages of each kind of device [7]. pMDIs include pros like cost-effectiveness, simplicity of usage, portability, and multi-dose content. As they require hand-breath coordination, however, their use in young children and the elderly may not be successful [8]. Most of the carbon footprint associated with current pMDIs comes from the propellants [9].

Since they can turn drug suspensions or solutions into tiny droplets that can aerosolize high doses of medications that DPIs or pMDIs cannot, nebulizers are important devices for the treatment of respiratory conditions. However, they can be difficult to carry, can be costly, are predominantly utilized by less mobile patients, need periodic maintenance, and require prolonged treatment times [7].

DPIs have been designed to overcome a number of the limitations of pMDIs and nebulizers, like the need for large compressors for nebulizer use and the possibility of systemic absorption in pMDIs [2]. The first DPI, named the Spinhaler, was developed in 1967 [10]. The Inhalator Ingelheim and the Cyclohaler were

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introduced in the 1980s and the beginning of the 1990s, respectively, after the debut of the Rotahaler in 1969 [11].

DPIs involve solid drug formulations. This offers superiority over other delivery devices when considering the active ingredient's stability, simplicity of usage, and delivered dose range. The possible risk of microbiological contamination, degradation, and decomposition is minimized with powder formulations in comparison to liquid ones since the active ingredient is in a powder state. DPIs don't contain propellant gas and don't require hand-breath coordination. When compared with other inhalation devices, DPI provides the highest intrapulmonary deposition [12].

Nevertheless, in certain situations, there are restrictions that limit the use of DPIs. First of all, in order to achieve a sufficient air flow rate to carry the drug particles adequately into the lung to act as intended, DPIs need patients to inspire with power. Regrettably, a patient's diminished lung function in numerous respiratory conditions results in inadequate airflow, which lowers the amount of drugs that are exposed to the lungs. Secondly, for the DPIs to function appropriately, storing and handling must be done correctly. Thirdly, a little variation in air humidity has an impact on the performance of DPIs, which in turn influences the clinical findings by decreasing the stability of the medications in the inhaler [13]. The hygroscopicity, size, shape, surface morphology, charge, and moisture content of dry powders are physiochemical characteristics that directly impact the aerosolization, bioavailability, and release from therapy devices of aerosolized medications. Dry powders used for inhalation are extremely tiny, difficult to aerosolize, and readily agglomerate owing to the cohesiveness of individual particles [14]. Various approaches, including milling, spray-drying, and spray-freeze-drying, have been developed to overcome the aforementioned difficulties [13].

In DPI formulations, the micronized API is typically combined with an inert carrier with the goal of enhancing the flowability and dispersion of API particles [15]. This carrier is frequently α-lactose monohydrate (commonly referred to as lactose). Lactose constitutes one of the limited excipients that the Food and Drug Administration (FDA) has authorized in inhalation therapy, and it is accepted for being safe. This makes it a good choice for the formulation of DPIs [16]. API plus lactose combinations have been referred to as either ordered or interactive mixtures, and they are easier for management throughout production operations compared to micronized API individually [2]. Conversely, the use of excipients frequently results in problems with blend uniformity as well as low drug loading. Delivering individuals a large-dose medication is a considerable difficulty [17]. Additionally, a small number of substances authorized for inhalation are included in the FDA's list of inactive components [18]. That's why the manufacturing of high-dose DPI formulations without carriers is needed and has been the topic of significant investigation in recent times [17].

A carrier-free system is an efficient and innovative approach to preparing formulations that generates a microsized end product with a limited range of particle size and low density by combining the active agent and additives [19]. The prevalent goal of the research and development of carrier-free DPIs is to optimize delivery and dispersion through the inhaler while minimizing particles' intrinsic cohesiveness [15].

This review's purpose is to examine DPIs, highlighting carrier-based and carrier-free DPI compositions, alternative delivery systems, and production technologies for DPIs.

1.1. DPI Formulations

DPI formulations can be broadly classified into two categories: conventional carrier-based and novel carrier-free formulations. The commercially available products are generally conventional carrier-based formulations that combine a micronized active therapeutic component with a large carrier (such as lactose) [20].

1.1.1. Production technologies for DPIs

Inhalable particles have been produced by milling, spray-drying, or spray-freeze-drying. A typical example of a traditional process for reducing the size of solid particles is milling. The production of excipient-free inhalation powders has been accomplished through the effective implementation of spray-drying [21]. Spray-drying has become an essential component of the drug industry in spite of its technological difficulties when applied on an industrial scale [22].

Milling

The method of physically converting larger particles to smaller particles with the use of mechanical energy is known as milling [23]. The drug industry has historically employed milling to enhance the physical

and pharmacological characteristics of their medications, including solubility, stability, and bioavailability [24]. For pulmonary administration of drugs by inhalation, milling has been widely employed in order to produce particles for inhalation with an acceptable particle size range. The fundamental benefits associated with the milling method are that it is low-cost, repeatable, and very simple to scale up. By modifying the particle's shape and surface characteristics, milling can influence a powder particle's hydrophobicity as well as flowability. Various milling methods generate various stresses over the solid particles that could lead to various surface energies. However, given some disadvantages regarding the milling technique, namely its inadequate control over particle size, size distribution, shape, and crystallinity, this technique doesn't seem especially appropriate to enable the reasonable manufacturing of particles for inhalation. Because of the related surface energy alterations, it may result in tightly adhering agglomerates and weakly dispersing powders. Over the particle surface, milling may also generate amorphous, unstable areas [21].

Hammer mills, jet or fluid-energy mills, ball mills, and colloid mills may all be employed for transforming coarse particles into inhalable powders [25]. Jet milling is the most widely utilized milling technique for developing an inhalable powder [26].

A study investigates the manufacturing of a respirable clofazimine formulation by employing the technique of air jet milling. Lacking a requirement for extra carrier particles or excipients, the jet milled formulation dispersed easily from an inhaler. Findings from this research point out that jet milling is a feasible production technology to manufacture clofazimine formulations intended for pulmonary administration [27].

Freeze-drying (Lyophilization)

Lyophilization is a drying technique that involves sublimating the product's water after it has been frozen [28]. A procedure called "lyophilization" or "freeze-drying" is used to create products that "love the dry state" [29]. Lyophilization produces porous and amorphous particles by entirely eliminating the solvent from the solution during the initial freezing stage. It consists of three stages: (i) droplet production; (ii) primary freezing; and (iii) sublimation drying. Since sublimation takes place at lower pressure, it can be applied to thermolabile substances like peptides and proteins. An extremely low temperature between -50 and -54 degrees Celsius is employed in lyophilizations' drying phase, which might physically harm the formulation's structure. Cryoprotectants, including amino acids and disaccharides, serve as protection against this [30].

There is enhanced long-term stability in the freeze-dried solid form since physical or chemical degradation processes are prevented or suitably slowed down. Freeze-dried formulations have the additional advantage of being easier to handle during shipment and storage [31]. Lyophilization's drawbacks include a prolonged period of processing, high energy prices, and expensive equipment capital costs [32].

Inhalable budesonide microparticles were created by applying the spray-freeze-drying technique. Budesonide-micronized porous particles were manufactured using hydroxypropyl beta-cyclodextrin (HPβCD) and L-leucine (L-leu) as excipients. The final particles exhibited an acceptable mass median aerodynamic diameter (MMAD) and an enhanced fine particle fraction (FPF). When compared to other formulations, their aerosolization performance and dissolution rate were also strengthened [30].

Spray-drying

A popular method of developing medicinal powders with nano- to micrometer-sized particles is spray-drying. Since it makes it possible to modify and regulate characteristics including flowability, moisture content, shape, density, crystallinity, dispersibility, particle size, and distribution of the powders, it has been extensively utilized for the inhalable particles' manufacturing [33].

In just one stage of the production procedure, spray-drying transforms a liquid feed into a dry powder state. The atomization of liquid feed into tiny droplets as well as the solvent's evaporation with the use of a hot drying gas are the fundamental concepts underlying the procedure. The procedure consists of the following four stages: preparing the liquid feedstock; atomizing the feed via a nozzle and contacting the hot drying gas; forming particles through evaporative mass transfer of the liquid from the droplet into the drying gas; and, finally, separating the dried product from the gas [33].

Spray-drying is the most commonly used technique for producing powder [34]. As it is quick, continuous, repeatable, single-step, and scalable without requiring significant adjustments, this technique is often highly attractive in both laboratory and industrial settings [35]. It is capable of manufacturing greatly

dispersible powders in the 1–5 µm size range that are suitable for inhalation [36]. Even with all of the benefits this technology offers, the yield relies substantially on the work scale when using standard spray-dryers. Because of this, yields are higher in larger-scale setups because the percentage lost makes up a smaller portion of the overall production volume. However, yields in laboratory settings are still far from ideal, with yields ranging from 20 to 70 percent. Usually, product loss in the drying chamber's walls is the cause of low yield [35].

Through spray-drying the neat naringin from various ratios of water/ethanol solvent systems, naringin microparticles were produced. This study illustrated that spray-drying solutions of pure naringin, with considerate selection of the optimal drug percentage and water/ethanol feed ratio, were capable of producing dry powder that has favorable aerodynamic performance. It appears that naringin particles suitable for airway deposition can be generated easily via spray-drying [37].

Electrospray

For the generation of particles of a particular size, electrospray is a novel technique. In such a scenario, a medication or polymeric solution is exposed to a significant potential difference, which causes the liquid to separate into droplets. The medication is then obtained as dry powder particles when the solvent evaporates. For DPI formulations, electrospray microparticle engineering offers various benefits. To achieve a suitable size range, several parameters (including solvent, concentration, potential, and flow rates) can be modified, and in a lot of circumstances, the addition of excipients, stabilizers, and surfactants is not necessary [38].

The capacity to form strongly charged, monodisperse particles is what makes the electrospray method distinctive [39]. Despite its uncommon application in the production of inhalable particles, electrospray holds considerable promise as a particle engineering process for fabricating inhalable lactose that has a substantially elevated FPF [40].

Although it is an appealing approach, electrospray has some drawbacks when it comes to particle manufacturing. One of the main issues is that the large number of process and instrument parameters might make optimization extremely difficult [41]. Another problem with electrospray is the limited quantity of particles obtained [42].

Budesonide and montelukast were combined to generate excipient-free DPI formulations through electrospray. According to the study's findings, electrospray is a successful particle engineering method that may be applied for producing DPI formulations [43]. A different study employed electrospray to produce excipient-free azithromycin microparticles. Based on the results, this method suggests an effective approach to developing excipient-free microparticles that are appropriately sized for direct pulmonary delivery of azithromycin via DPI devices [38].

1.1.2. Alternative delivery systems for DPIs

In order to achieve local and systemic targeted therapy for a variety of diseases, including cancer therapy, diabetes, and respiratory conditions, particulate-based pulmonary drug delivery systems present promising prospects. Different particulate-based pulmonary drug delivery systems have been made with a variety of carriers in an effort to optimize the loading of drugs, residence half-life, drug release, and toxicity while also overcoming multiple lung clearance mechanisms, enzymatic breakdown, and rapid systemic absorption [44]. Liposomes, microparticles, and nanoparticles are the most commonly employed delivery systems for inhalation [45].

Liposomes

Liposomes comprise lipid bilayers containing active ingredients. Lipid bilayers may be one or more [45]. In view of their potential benefits, which involve less local irritation, biocompatibility, biodegradability, and sustained drug release, liposomes are currently gaining attention in studies on pulmonary drug delivery [44]. As liposomes are highly tolerated and nonimmunogenic in humans, liposome-encapsulated medications appear to be a viable approach for targeting the lung. Immune cells, such as macrophages, have the ability to phagocytose liposomes, which makes it possible to direct antimicrobials and other therapeutic substances toward these immune cells. Since liposomes may be made with ingredients that are naturally found in the lungs, like dipalmitoylphosphatidylcholine (DPPC), a compound that makes up 70 to 80 per cent of the structure of lung surfactants, they are suitable systems for pulmonary drug delivery. It has been demonstrated that pharmaceutical drug encapsulation in liposomes enhances the therapeutic effect of the medication [46]. Table 1 shows some examples of published studies on liposomal DPIs.

In Table 1, three different liposomal DPI studies were indicated. Patel et al. manufactured a liposomal DPI containing sorafenib tosylate. Liposomes were produced via the thin-film hydration technique. Following that, through spray-drying, liposomes were generated into DPI. With an Andersen Cascade Impactor (ACI), formulations were tested and compared to conventional DPI for *in vitro* lung deposition. According to the findings, the FPF% of conventional DPI was 49.98 ± 0.07, and the FPF% of formulated DPI was 83.7 ± 0.09. The formulated DPI's enhanced deposition pattern may be attributed to the particles' homogeneous size distribution and spherical shape. A pitted surface having fewer areas of contact and showing better de-agglomeration from the carrier might also be another factor to explain this outcome [47].

Lee et al. fabricated lysozyme-loaded liposomal DPI formulations. The process of thin-film hydration was implemented to develop liposomes, which were then homogenized under high-pressure. Finally, spray-drying was applied in order to obtain liposomal DPI formulations. Several non-ionic surfactants, such as sucrose stearate, poloxamer 407, poloxamer 188, and polysorbate 80, were used to formulate liposomal DPIs. Through the Next Generation Pharmaceutical Impactor, the aerodynamic characteristics of formulations were evaluated. The FPF% varied from 10.98 to 28.36, based on the results. The best aerosol performance was observed in two formulations: one containing polysorbate 80 and the other containing sucrose stearate. In these two formulations, the lysozyme/surfactant (w/w) ratio was 1/0.5. When the lysozyme/surfactant (w/w) ratio was 1/5, a lower FPF% was obtained. This situation was shown in three formulations containing polysorbate 80, poloxamer 188, and poloxamer 407, respectively. This data suggests that when surfactant concentrations are elevated, aerosol performance is negatively influenced. On the other hand, the formulation containing sucrose stearate as a surfactant revealed good aerosol performance. The lysozyme/surfactant (w/w) ratio was again 1/5. The lubricant function of sucrose stearate is the reason for it [48].

Honmane et al. conducted another study related to liposomal DPI. Thin-film hydration was the method applied in this study for forming the liposomes. Then, following a spray-drying process, liposomes were converted to liposomal DPI. Maltodextrin or lactose were used as carriers in formulations. An ACI was employed to assess the formulations' *in vitro* lung deposition. The FPF% value of spray-dried liposomes with maltodextrin was 44.68 ± 0.57, and the FPF% value of spray-dried liposomes with lactose was 64.01 ± 0.43. This outcome demonstrated that the formulation containing lactose outperformed the formulation containing maltodextrin in terms of aerosol performance [49].

Microparticles

Small solid particles or liquid medication droplets, measuring between 1 and 1000 µm in size, are known as microparticles. These particles are trapped in walls made of either synthetic or natural polymers with varying thicknesses. Their form is basically spherical. In the last few years, microparticles have gained attention due to their advantages over other traditional and modern drug delivery methods. These advantages include a drug's increased relative bioavailability, stability, and longer shelf life; the need for fewer doses to achieve therapeutic benefit; a lower risk of toxicity and side effects; controlled and sustained drug release for an extended time; targeted drug delivery; compatibility with medications that have low gastrointestinal tract absorption and inadequate solubility; lower immunogenicity; live cell encapsulation; higher drug loading along with entrapment efficiencies; as well as improved patient compliance. However, the drawbacks of microparticles are as follows: they are challenging to fabricate on a large scale; the drug gets inactivated or degraded within the manufacturing process; and the drug's release rates are difficult to manage [45]. Table 2 shows some examples of published studies on microparticle-based DPIs.

Table 2 lists four distinct investigations pertaining to the formulation of microparticle-based DPIs. Hu et al. fabricated curcumin-loaded microparticles via freeze-drying after the emulsion/evaporation technique. A Next Generation Impactor (NGI) was utilized to simulate the deposition of microparticles in the lungs. The lung deposition of curcumin microparticles, curcumin powders, and curcumin/lactose powders was evaluated at flow rates of 60 L/min and 30 L/min. At a flow rate of 60 L/min, the FPF% of curcumin microparticles was 13.41 and the FPF% of curcumin powders was 7.54. At a flow rate of 30 L/min, the FPF% of curcumin microparticles was 7.41, the FPF% of curcumin powders was 3.78, and the FPF% of curcumin/lactose powders was 1.69. The fundamental cause might be the cylinder-shaped curcumin crystals and curcumin powders' intense adsorption on lactose powders owing to their electrostatic interaction. Consequently, when compared with curcumin powders and curcumin/lactose powders, curcumin microparticles demonstrated substantially superior lung deposition [50].

Mezzena et al. formulated solid lipid microparticles containing budesonide. Oil-in-water emulsification was the process to manufacture the microparticles, and spray-drying came next. A comparison was carried out between the budesonide microparticles and conventional spray-dried crystalline and amorphous budesonide samples. With the help of a Multistage Liquid Impinger (MSLI), the aerosolization performance was determined. For crystalline budesonide particles, the FPF% value was 29.5 ± 0.3, and for amorphous budesonide particles, the FPF% value was 27.3 ± 2.1. The dissimilarity in metastability might be responsible for the variation in the FPF between amorphous and crystalline samples. For budesonide microparticles, the FPF% value was 21.1 ± 0.6. There could be a number of reasons for the solid lipid microparticles' decreased FPF in comparison to the spray-dried budesonide samples. First, at comparatively low temperatures, the solid lipid microparticles encounter a number of phase transitions. In comparison to budesonide alone, the basic reason for this phase alteration could give rise to increased instability and, hence, greater interparticulate adhesion. Second, in contrast to the spray-dried budesonide solutions, which were spherical in shape, the solid lipid microparticles possessed an uneven morphology. As a result, according to the present study, the lipid-based system's drug packing and contact geometry might encourage more particle interlocking and, therefore, decreased aerosol performance [51].

Through freeze-drying following o/w emulsification, Scalia et al. produced microparticles loaded with quercetin. The *in vitro* aerosolization properties of microparticles were analyzed via a NGI. The FPF% value of microparticles was 20.5 ± 3.3. FPF is expressed as a percentage of drug concentrations that are acceptable for inhalation delivery and have an aerodynamic diameter of less than 4.46 μm. Based on the results, quercetin microparticles might be prepared as a dry powder that would be appropriate for administering drugs by inhalation [52].

In the study they performed, Kwon et al. applied a spray-drying method to turn bosentan-containing ethanol and water solutions into bosentan microparticles. Three different formulations with different ethanol concentrations—60%, 80%, and 100%, respectively—were prepared. The ACI was used to determine the microparticles' *in vitro* aerosol behavior. The formulation containing 60% ethanol had a FPF% of 59.97 ± 5.45, the formulation containing 80% ethanol had a FPF% of 59.47 ± 10.46, and the formulation containing 100% ethanol had a FPF% of 21.04 ± 11.75. According to the scanning electron microscopy analysis, the formulation containing 60% ethanol showed a rough surface with corrugated morphology; the formulation containing 80% ethanol showed a rough surface with spherical morphology; and the formulation containing 100% ethanol showed a smooth surface with spherical morphology. Additionally, the aerodynamic sizes of formulations containing 60% ethanol, 80% ethanol, and 100% ethanol were 1.27, 1.27, and 6.95 μm, respectively. The findings indicate that microparticles with a rougher surface and smaller particle size aerosolized more effectively than those with a smoother surface and bigger particle size (FPF%: 21.04 ± 11.75, 59.47 ± 10.46, and 59.97 ± 5.45 for formulations containing 100% ethanol, 80% ethanol, and 60% ethanol, respectively) [53].

Nanoparticles

Drugs in the form of solid particles or particulate dispersions with sizes that vary between 10 and 1000 nm are known as nanoparticles. These particles are mostly composed of biocompatible and biodegradable polymers, either synthetic or natural [45]. Nanoparticles play a role in improving biodistribution, penetration across biological barriers, stability *in vivo*, and bioavailability. They additionally offer targeted and controlled drug release. Through modifying a drug's pharmacokinetic and pharmacodynamic characteristics, nanoparticles can promote its therapeutic index [2]. Table 3 shows some examples of published studies on solid lipid nanoparticle-based DPIs.

Four distinct published studies on DPIs based on solid lipid nanoparticles are displayed in Table 3. Dolatabadi et al. developed an alendronate solid lipid nanoparticle-loaded DPI formulation. By employing a hot homogenization method, solid lipid nanoparticles were formed, and then spray-drying was performed to generate DPI. The spray-drying process was carried out with or without mannitol. The NGI was implemented to conduct an *in vitro* aerosolization study. In the DPI formulation without mannitol, the FPF% value was 11.87, while in the formulation with mannitol, the FPF% value was 9.03. The substances' varying hygroscopicities and surface characteristics, as well as the existence of particles that agglomerate in the air stream during inspiration via the inhaler, could be the reason for the small differences [54].

Maretti et al. designed solid lipid nanoparticle assemblies loaded with rifampicin. The melt-emulsifying method and freeze-drying were utilized for the fabrication of formulations. Sixteen formulations were manufactured with four different formulation parameters. These included the type of cryoprotectant (trehalose or mannitol), the concentration of cryoprotectant (1/0 or 1/1.5 w/w), the water dilution (1/0 or

1/100 v/v), and the pre-freezing temperature (-20 °C or -70 °C). The Fast Screening Impactor was a device to examine the *in vitro* aerodynamic performance of formulations. The range of percentages of the respirable fraction (RF) values was around 8.77 to 70.40. Out of the sixteen formulations, only five exhibited RF values higher than 40%, which is a minimum value associated with an inhaled product's respirability. Sample dilution played the primary role in the *in vitro* aerodynamic performance, with pre-freezing temperature and cryoprotectants additionally playing a significant role. Raising the sample dilution progressively raised the *in vitro* respirability. When freezing at -70 °C without the use of cryoprotectants, the highest level of water dilution resulted in the largest RF, around 60%, whereas the lowest water dilution produced the largest RF, around 35% under the same circumstances. When the freezing temperature was -20 °C and the water dilution was at its highest level, solely trehalose was capable of reducing inhalation [55].

In another study, Nemati et al. investigated ethambutol-containing solid lipid nanoparticles. Hot homogenization and ultrasonication were the two processes for creating ethambutol-loaded solid lipid nanoparticles. Solid lipid nanoparticles containing ethambutol, both with and without mannitol, were spray-dried in order to generate DPI formulations. Via a NGI, the dry powders' aerodynamic properties were assessed. The dry powders lacking mannitol had an FPF% of 23.98 ± 0.38, and the dry powders containing mannitol had an FPF% of 30.91 ± 0.77, in accordance with the findings gathered. The FPF% of the mannitol-containing DPI is greater than that of the powder lacking mannitol. The variations in size, moisture content, surface characteristics, and the presence of agglomerated particles in the air during inspiration through inhalation could all be contributing factors to this difference [56].

Through the application of the double emulsion method, Li et al. formed solid lipid nanoparticles, which included thymopentin. Then spray-drying was done to convert solid lipid nanoparticles to inhalable microparticles. Implementing a twin stage impinger, the aerodynamic features of the microparticles were examined. The microparticles exhibited a RF of 51.07% ± 1.21% and an emitted dose of 98.0% ± 1.23%. This outcome reveals that the microparticles' aerodynamic features were acceptable for lung delivery [57].

1.1.3. Excipients used in DPI formulations

Excipients have the potential to enhance the performance of DPI formulations even more. Excipients are frequently used in DPI formulations for the following four reasons: (a) improving a drug's mechanical characteristics; (b) improving a drug's chemical and physical stability; (c) adjusting a drug's pharmacokinetics or pharmacodynamics; (d) by acting as a powder flow enhancer and bulking agent to increase the dose reproducibility. Excipients ought to be inert as well as non-therapeutic when administered at the recommended dose [18]. Currently, the FDA has authorized only a very few excipients regarding respiratory drug delivery. DPI formulations do not typically include excipients that are utilized in nebulization and pMDI formulations like polysorbates, sorbitan trioleate, and oleic acid due to the low melting points as well as semi-solid or liquid states [6].

Excipients used in carrier-based DPIs

DPI formulations are manufactured by solvent extraction/evaporation, phase separation (coacervation), jet milling, supercritical fluid, ball milling, high-pressure homogenization, spray-drying, and spray-freeze-drying methods, and modifying and/or combining these methods. The most commonly applied method is spray-drying [12].

The inadequate flowability and aerosolization characteristics of micronized APIs are one drawback of DPIs. One typical approach to getting around this challenge is to combine the API with excipients that can give the powder mixture the appropriate flow characteristics. Lactose, mannitol, and glucose are the excipients that are currently authorized for pulmonary delivery. These commercially accessible compounds have specific particle sizes, shapes, and roughness. They serve as carriers to enhance flowability and aerosolization by lowering the cohesive forces between micronized API particles [58]. Additionally, with the utilization of biodegradable polymers, targeted delivery of drugs and sustained release are made possible. Chitosan is a biodegradable polysaccharide that is non-toxic. It is extremely mucoadhesive because of its polycationic composition. Moreover, it is established that chitosan interacts with macrophage-expressed mannose receptors. Hence, with the incorporation of chitosan, pulmonary retention of inhalation formulations may be enhanced [18]. Besides, the controlled release of a variety of drugs, such as antibiotics, peptides, proteins, and anti-asthmatic drugs, has been accomplished through the employing of PLGA microspheres in pulmonary administration [6]. The reason for the sustained release of drugs from PLGA particles is PLGA's extremely slow rate of breakdown [18].

Table 1. Examples of published studies on liposomal DPIs

Drug	Method of Preparation	Main Ingredients	Capsule Fill	Air Flow Rate	Testing Device	Inhaler	FPF %	Reference
Sorafenib tosylate	Spray-drying after thin-film hydration	Liposome constituents: Phosphatidylcholine (Phospholipon 90H) and cholesterol Liposomal DPI additives: Mannitol and leucine	30 mg	28.3 L/min	ACI	Revolizer	83.7 ± 0.09	[47]
Lysozyme	Thin-film hydration followed by high-pressure homogenization and spray-drying	Liposome constituents: Phosphatidylcholine, cholesterol, non-ionic surfactants (polysorbate 80, poloxamer 188, poloxamer 407 and sucrose stearate) Liposomal DPI additives: Lactose	30 mg	60 L/min	Next Generation Pharmaceutical Impactor	Breezhaler	up to 28.4	[48]
Salbutamol sulfate	Spray-drying after thin-film hydration	Liposome constituents: Soyaphosphatidyl choline and cholesterol Liposomal DPI additives: Maltodextrin or lactose	powder containing drug equivalent to 200 µg of salbutamol sulfate	60 mL/min	ACI	Rotahaler	64.01 ± 0.43 (with lactose) 44.68 ± 0.57 (with maltodextrin)	[49]

Table 2. Examples of published studies on microparticle-based DPIs

Drug	Method of Preparation	Main Ingredients	Capsule Fill	Air Flow Rate	Testing Device	Inhaler	FPF %	Reference
Curcumin	Freeze-drying after the emulsion/evaporation method	Poly(lactic-co-glycolic acid) (PLGA), polyvinyl alcohol (PVA) and ammonium bicarbonate	30 mg	60 and 30 L/min	NGI	Twister	13.41 (60 L/min) 7.41 (30 L/min)	[50]
Budesonide	Spray-drying after oil-in-water emulsification	Pluronic F-68 and Compritol 888	11 mg	60 L/min	MSLI	Aerolizer	21.1 ± 0.6	[51]
Quercetin	Freeze-drying after o/w emulsification	Tristearin and phosphatidylcholine	10 ± 0.1 mg	60 L/min	NGI	Aerolizer	20.5 ± 3.3	[52]
Bosentan	Spray-drying	-	10 mg	60 L/min	ACI	Handihaler	59.97 ± 5.45	[53]

Table 3. Examples of published studies on solid lipid nanoparticle-based DPIs

Drug	Method of Preparation	Main Ingredients	Capsule Fill	Air Flow Rate	Testing Device	Inhaler	FPF %	Reference
Alendronate	Spray-drying after the hot homogenization method	Compritol 888 ATO, Tween 80, Poloxamer 407 DPI additives: Mannitol	25 mg (without mannitol) 30 mg (with mannitol)	60 L/min	NGI	Easyhaler	11.87 (without mannitol) 9.03 (with mannitol)	[54]
Rifampicin	Freeze-drying after the melt-emulsifying method	Stearic acid and sodium taurocholate Cryoprotectant: Trehalose or mannitol	10 mg	60 L/min	Fast Screening Impactor	RS01	>50	[55]
Ethambutol	Spray-drying after the hot homogenization process and ultrasonication	Compritol, Tween 80 and poloxamer DPI additives: Mannitol	100 mg (without mannitol) 120 mg (with mannitol)	60 L/min	NGI	NA	23.98 ± 0.38 (without mannitol) 30.91 ± 0.77 (with mannitol)	[56]
Thymopentin	Spray-drying after the double emulsion method	Sodium cholate, glyceryl monostearate, soybean phosphatidylcholine, poloxamer 188 DPI additives: Mannitol and leucine	NA	60 L/min	Twin Stage Impinger	NA	51.07 ± 1.21	[57]

In recent years, lactose has been the excipient that commercial DPIs have used the most. It has a well-known stability and safety profile. For the production of inhalation lactose, various procedures are employed [6]; including micronizing by milling, sieving, and blending [59]. In pharmaceutical-grade lactose, purity and other physical characteristics are also strictly controlled, and it is economical and readily accessible in a variety of grades [6].

The production and characterization of lactose for inhalation have been the subject of a considerable amount of written literature. However, lactose cannot be utilized for delivering medications to diabetic individuals owing to clinical issues. Meanwhile, due to its ability to reduce sugar, which might interfere with either drug's or protein's functional groups, lactose monohydrate may not be the most suitable carrier for some active ingredients (such as formoterol) or for particular drug classes (such as peptides or protein drugs). Furthermore, transmissible spongiform encephalopathy (TSE) continues to become a problem for lactose monohydrate since it is made from bovine milk or with additions that originate from bovine. A condition known as lactose intolerance requires the individual to utilize formulations lacking lactose [60].

As a lactose substitution in inhaled powders, the sugar alcohol mannitol has been researched extensively [18]. Salbutamol sulfate, which is hydrophilic, and budesonide, which is hydrophobic, were employed as model drugs in a study that aims to evaluate how the physicochemical characteristics of a carrier can influence *in vitro* lung deposition. In the inhalation powders, lactose, mannitol, and glucose were employed as carriers for budesonide, and mannitol and glucose were employed for salbutamol sulfate. The outcomes indicated that when mannitol served as a carrier, the highest RF of budesonide were attained. Moreover, when mannitol was used as the carrier rather than glucose, the RF of salbutamol sulfate appeared to be higher [61]. Mannitol is compatible with drugs including amines since, in contrast to lactose, it is a non-reducing substance. It is not the best stabilizer, though, as mannitol usually crystallizes quickly following spray-drying. Yet, mannitol may be utilized in the role of stabilizer despite having a low glass transition temperature if it is combined with various other ingredients (including salmon calcitonin, glycine, inorganic salts, and various sugar-derived compounds), which either adequately raise the system's glass transition temperature or prevent crystallization via alternative mechanisms. The first authorized inhalable insulin formulation for human, Exubera, which contains sodium phosphate, mannitol, glycine, and sodium citrate as ingredients, served as an instance of this [18]. Mannitol, a polyol, is commonly utilized in freeze-drying [62].

Trehalose, with a glass transition at a temperature of around 106 degrees Celsius, exists as a non-reducing disaccharide comprising two molecules of glucose. These properties allow trehalose to generate a glassy sugar matrix that stabilizes biopharmaceuticals in powders for inhalation that have been spray-dried. Amorphous sugars' hygroscopicity following spray-drying is a significant disadvantage, even though they may help stabilize biopharmaceuticals in formulations for inhalation. As a result, during transportation and storage, formulations with trehalose are more likely to recrystallize and become cohesive. Trehalose will thus probably need to be mixed with additional ingredients, specifically moisture protectors (such as an aminoacid derivative, tri-leucine) [18].

In inhalation therapy, controlled drug delivery techniques are starting to look more and more interesting. As prospective controlled drug delivery formulations for the lung, a variety of carrier systems have been designed and evaluated [6]. Typically, these systems consist of polymer-based microparticles or nanoparticles loaded with drugs that are encapsulated within a microparticulate matrix. This matrix consists of various excipients (such as sugars). Two common biodegradable polymers are PLGA and chitosan [18]. Table 4 shows some examples of published studies on biodegradable polymers for inhalation. As can be seen in the table, PLGA is generally used in the double-emulsion method.

Systemic absorption enhancers may be necessary, depending on the powder's desired delivery site. In order to enhance the systemic absorption of medications, some excipients have been suggested [63]. Aqueous solubility, systemic absorption, and drug bioavailability have all been found to be enhanced via the incorporation of cyclodextrines in pulmonary drug administration. Proteins, including human growth hormone, insulin, cyclosporine A, and others, have been revealed to be delivered through the lungs more effectively when cyclodextrines are present. Bile salts from the group of surface active agents, like taurocholate, taurodeoxycholate, deoxycholate, cholate, and glycocholate sodium salts, are frequently used as absorption enhancers [6].

Excipients used in carrier-free DPIs

In the last several years, the production of carrier-free DPIs has attracted increased interest [68]. The inclusion of a large carrier is unnecessary in carrier-free DPIs thanks to the utilization of particular technologies (such as co-spray-drying) and excipients (like L-leu) [69].

Numerous investigations have confirmed that leucine-containing DPIs for pulmonary delivery are safe, despite the fact that leucine has not been authorized for use in inhalation products. For instance, a number of *in vitro* cytotoxicity tests have supported the DPI formulations' safety for pulmonary delivery that include 20% w/w leucine. The powder appears safe for inhalation as it did not show any cytotoxic effects on lung epithelia cell lines (A549 and Calu-3) or alveolar cell lines (NR8383) [70].

Table 4. Examples of published studies on biodegradable polymers for inhalation

Drug	Preparation Method	Main Ingredients	FPF %	Reference
Insulin	Double emulsion	PLGA and HPβCD	26.9–89.6	[64]
Gentamicin sulfate	Double emulsification-solvent evaporation	PLGA	39	[65]
Voriconazole	(w/o/w) double emulsion	PLGA or polylactic acid (PLA) , ammonium bicarbonate, PVA	27.3 ± 2.7	[66]
Prothionamide	Ionic gelation	Chitosan and sodium tripolyphosphate	81.19	[67]

Leucine-containing DPI formulations have additionally been found to be tolerable and safe in a number of clinical trials. For the management of group 1 pulmonary arterial hypertension, leucine was the only excipient used in the formulation of the seralutinib DPI. In a Phase IA clinical trial, the bioavailability, safety, and tolerability of single and multiple ascending inhalation doses were evaluated. The seralutinib DPI passed this trial with success. Phase IB and Phase II clinical trials are now being conducted on seralutinib DPI [70].

In a Phase II clinical trial, trospium chloride inhalation dry powder (prepared in leucine with DPPC or sodium saccharin) was found to be safe, effective, and tolerable when delivered in single doses to individuals suffering from chronic obstructive pulmonary disease (COPD) [70].

Phase I clinical trials for capreomycin inhalation powder, which was combined with leucine at an 80:20 ratio, concluded with success. The tolerability and safety of inhaling nominal doses of 25, 75, 150, or 300 mg of capreomycin in healthy volunteers were examined in this study. Each participant exhibited a good tolerance for the powders inhaled. Leucine's appropriateness for pulmonary drug delivery is strongly supported by these *in vitro* and clinical investigations [70].

Recent studies have demonstrated that amino acids may reduce hygroscopicity while enhancing particles' charge density and surface activity. It has been proven that adding different amino acids to inhalation formulations greatly enhances the dry powder's *in vitro* deposition profile [6]. When leucine exists within formulations, corrugated particles often form. This lowers the adhesive and cohesive forces between particles as well as their aerodynamic diameter. As a result, the dispersibility and flowability of aerosolized particles enhances [71]. L-leu has been utilized as a dispersibility enhancer in DPI formulations containing sildenafil, and it has been informed that this greatly improves the aerodynamic performance of powders [72].

It has been demonstrated that drugs can be delivered to the lungs via porous microparticles [73]. Due to their superior flow properties and lower interparticulate attractive forces compared to micronized drug materials, these particles have been presented as favorable for drug administration to the respiratory system through oral inhalation. Their small aerodynamic diameters relative to their geometric diameters and low bulk densities enable higher deposition in the lower respiratory area [74]. The PulmoSphere™

technology designed for DPI formulation in the last years of the 1990s serves as an important historical instance for porous particles. The porous particles developed via PulmoSphere™ technology consist of lung surfactant (distearoylphosphatidylcholine, DSPC), surface modifier, and pore-forming agent (such as perfluorocyte bromide). It has been shown to be applicable for integrating medications into PulmoSphere particles, including ciprofloxacin, tobramycin, budesonide, and indacaterol [75]. Porous microparticles of bendroflumethiazide were produced through spray-drying ethanolic or methanolic drug solutions containing ammonium carbonate, which functions as a pore-forming agent. This novel approach was used to generate the porous microparticles [74].

2. DISCUSSION

The negative environmental effects of respiratory inhalers, which contain propellants, are becoming more widely recognized among both patients and healthcare providers. pMDIs create a substantial carbon footprint owing to the propellants' tendency to cause global warming and the frequent usage of inhalers [76]. Since the patient's own inhalation disperses the powder, DPIs, on the contrary, do not need a propellant. Another propellant-free alternative that has gained popularity is the soft mist inhaler (SMI). Nebulizers can additionally be utilized; in an investigation comparing a nebulizer to a pMDI, the nebulizer's carbon footprint was determined to be considerably less [9].

The environmental effects of inhaled drugs are being taken seriously by a growing number of international and national organizations. Ozone-depleting compounds must be phased out of manufacturing and consumption, according to the 1987 Montreal Protocol. The National Health Service's (NHS) Sustainable Development Unit promotes the utilization of "lower carbon inhalers, like DPIs," in an effort to cut down on carbon emissions from pMDIs. Furthermore, the British Thoracic Society has made a commitment to lower the carbon footprint of inhaled therapeutics and suggests prescribing "low carbon options" to pMDIs, like DPIs and reusable SMIs [9].

The lungs have a restricted ability for buffering, as opposed to the gastrointestinal tract. Various substances that have the opportunity to improve drug delivery outcomes additionally carry the risk of irritating or injuring the lungs [77]. An ongoing issue in the development of DPI formulations is excipients' pulmonary toxicity. Excipient toxicity is usually not well understood because toxicity studies are generally quite expensive and pulmonary drug delivery is an unconventional route of administration [18]. In this regard, the variety of possible excipients is restricted to substances that are found naturally in the lung and that are quickly removed or metabolized [77]. The FDA's list of inactive ingredients for inhalation only contains a small number of substances, which illustrates this [18].

Inhalable formulations based on novel drug delivery systems are reported to be effective in managing a variety of respiratory conditions. These formulations include liposomes, nanoparticles, and microparticles. In order to facilitate the delivery of drugs to the lungs, natural polymers, including polysaccharides, albumin, gelatin, and chitosan, are frequently utilized. For the inhalation formulations, numerous biodegradable and biocompatible synthetic polymers are accessible, along with natural polymers. These involve PLGA, PLA, polycaprolactone (PCL), and polyglycolic acid (PGA). By reason of their alluring mechanical and processing characteristics, PLA and PLGA are the polymers that are most commonly employed in inhalable formulations. The US Food and Drug Administration (USFDA) and the European Medicines Agency (EMA), two international regulatory organizations, judge PLGA safe for application in pharmaceutical products delivered orally and parenterally. Nevertheless, the FDA has not granted PLGA approval for delivering drugs by inhalation [78].

Prior to introducing novel excipients for inhalation, comprehensive toxicity evaluations in rats and non-rodents must be performed. The regional accumulation of the polymers and their broken-down constituents, which gradually break down or are eliminated in the lungs, could be toxic to the lungs. Hence, these polymers should not be included in formulations prepared for inhalation. According to certain investigations, PLGA particles can remain in the mouse lungs for twenty days or more. The long-term toxicological effects of inhaling PLGA particles, however, are still not extensively studied. Glycolic acid and lactic acid, two of the acid breakdown components of PLGA, have the possibility of causing irritation to the lungs. It is imperative to obtain long-term toxicological findings regarding PLGA inhalation [78].

In the marketplace currently, carrier-based formulations generate the majority of DPIs. Nonetheless, the average FPF of these formulations is between 20 and 30 percent, indicating that the drug only partially accesses the lungs' deeper layers [69]. In the last several years, the production of carrier-free DPIs has

received more attention [68]. Due to their superior aerodynamical characteristics, which contribute to a considerable deposition of drugs in the alveolar areas, carrier-free systems are noteworthy [19].

3. CONCLUSION

The pulmonary administration of drugs using DPIs is becoming increasingly important today, and new studies are being carried out on this subject. Most DPIs on the market contain carriers; however, carrier-free DPI formulations have been produced in recent years in order to eliminate the problems caused by carriers. The excipients utilized vary depending on whether the DPI contains or does not contain a carrier. In carrier-free DPIs, amino acids or pore-forming agents are generally utilized instead of carriers.

This paper reviewed the DPIs, categorized them as carrier-based and carrier-free, and explained the fundamental characteristics of the excipients used in. Alternative delivery systems such as liposomes, microparticles, nanoparticles, and production technologies for DPIs were also highlighted.

It is expected that carrier-free DPIs will be produced more intensively in the coming years due to the advantages mentioned in this article. Liposomes, microparticles, and nanoparticles will also continue to be investigated as DPI delivery systems.

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