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Development of dry powder inhaler formulations for drug delivery systems

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ABSTRACT: Oral or parenteral administration of drugs to treat lung diseases is met with several challenges, including delivery of the active substance in insufficient amounts, inability to produce the desired effect at the target region, and severe systemic side effects. The best solution to this problem is the pulmonary administration of drugs. Although several formulations for administering inhaled medications such as nebulizers and metered-dose inhalers are available, dry powder inhalers (DPIs) are particularly advantageous owing to their ability to administer a high amount of active ingredient in a short time and higher stability than that of aqueous formulations. Similar to all inhaler formulations, one of the major problems encountered in DPIs is the inability of the active substance to reach the peripheral lungs in sufficient quantity. Moreover, reproducible results are difficult to obtain due to different inhalation capacities among individuals. This review provides the readers with a general perspective on different approaches used in developing various DPIs. Moreover, the review discusses the aerodynamic parameters of these formulations. DPIs developed with novel manufacturing methods are safe with increased therapeutic efficacy, as demonstrated by the results of their *in vitro* and *in vivo* safety and efficacy studies. These findings indicate that DPIs could serve as a promising modality for pulmonary drug delivery.

KEYWORDS: Dry powder inhaler; pulmonary delivery; aerodynamic parameter; nanoparticle; polymeric dry powder inhalers; lipid-based dry powder inhalers.

1. INTRODUCTION

Several diseases such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic lung fibrosis, lung cancer, pneumonia, and tuberculosis are known to affect the lungs. Lung diseases require long-term treatment owing to their chronic nature; therefore, side effects may be observed during systemic drug administration [1, 2]. Several approaches, including chemical drugs, antibiotics, proteins, peptides, and genetic materials, are used to treat lung diseases. However, these approaches provide only symptomatic relief instead of complete treatment of diseases [2-4]. Therefore, the primary goal of researchers is to develop novel inhaler formulations to effectively treat lung diseases.

Over the past several years, administration of drugs through the respiratory system is a widely preferred approach to treat lung diseases; however, it requires considerable improvement. While the drug administered through the respiratory system exerts a rapid effect, it is difficult to predict and standardize it [5, 6]. Inhaler systems are widely used in acute and chronic diseases owing to a large surface area and low enzymatic activity of lungs. The widespread use of inhaler systems is attributed to their rapid action and less systemic side effects in treating acute and chronic diseases, respectively.

Administration of drugs by inhalation is associated with several advantages such as minimization of systemic side effects since the active substance can be transported directly to the site of action in lower and upper respiratory tract diseases, thereby increasing the treatment efficiency. Moreover, pulmonary drug administration can overcome the biological barriers such as the first-pass effect and a regular clinical response. Another advantage is that the same therapeutic effect can be achieved at considerably lower doses than that obtained via the oral administration, with no influence of any condition that may reduce patient compliance, such as poor taste and pain. Drug substances ranging from small molecules to large peptide molecules can be delivered as inhaled formulations. Although inter-individual variability is observed, physiological conditions

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in the lungs, including the large surface area, highly permeable membrane structure, and low enzymatic activity, increase the effectiveness of inhaler formulations [7-16].

As the lungs are continuously exposed to pathogens and particles present in the inhaled air, several defense mechanisms, such as mucociliary clearance and phagocytosis, exist to protect the lungs from these threats. However, these mechanisms may also act as an obstacle to the pulmonary administration of drugs [17, 18].

In this context, an effective inhaler system should possess the following characteristics: repeatable dosing, chemical and physical stability, controlled inhalation of dose, use of a portable device, and effective particle size to reach the target region.

Although different inhaler systems, such as nebulizer and metered-dose inhaler, are available, dry powder inhalers (DPIs) provide enhanced stability and the highest amount of administered drug [19-21]. DPIs have been frequently used in the recent years to treat several local and systemic diseases and found to be superior over other formulations. This feature is attributed to the solid form of the active substance that provides enhanced stability, is easy to use, and can be administered in large doses. Moreover, other risks such as fragmentation, decomposition, and microbiological contamination of the dose, are less as compared with that in liquid formulations [19-21].

The therapeutic efficiency of DPIs is determined by their aerodynamic properties. These include the mass median aerodynamic diameter (MMAD), emitted dose (ED), fine particle dose (FPD), and fine particle fraction (FPF) of the produced formulations. ED refers to the dose that is released from the device upon inhalation, FPD refers to the dose reaching the target site in the lungs, and FPF refers to the fraction reaching the target site in the lungs. Although FPD and FPF generally identify particles smaller than 5 µm, this size may vary depending on the target area. The aerodynamic particle diameter is expressed as the diameter of a sphere of 1 g/cm^3 density having the same aerodynamic behavior as that of the particle and is calculated using the following equation.

$$d_A = d_V \sqrt{\frac{\rho}{\rho_0 X}} \qquad \text{Eq. 1}$$

where d_V is the volume equivalent diameter, P_0 is the unit density, P is the particle density, and X is the dynamic shape factor [22].

The ED, FPD, and FPF parameters are intended to be high and reproducible to achieve greater treatment efficacy by reaching the target site. Particles with an aerodynamic diameter of 1 to 5 µm can reach the depths of the lungs, whereas those with an aerodynamic diameter less than 1 µm are exhaled out. Particles with size larger than 5 µm get deposited in the tracheobronchial (>5 µm) and oropharynx (≥10 µm) areas [23]. Particle size distribution, density, shape, charge, hygroscopicity, and surface properties are other critical factors that define the area of deposition in the respiratory tract [24, 25].

The stability of DPIs should be performed as recommended in ICH Q1A(R2), Q1C, Q1D, and Q1E [26-30]. During the stability studies, the DPIs should be stored in upright, horizontal, and inverted. If the DPI position does not affect the quality, stability tests can be performed on the DPI recorded at one position. If data indicate that a particular orientation is detrimental to product stability, that orientation should be used for stability studies. If the DPI product has a secondary packaging, the time that the product can be used after removal of the protective packaging should be determined in accordance with the stability results. DPI should be removed from the protective packaging at the end of its shelf life, and the pharmaceutical product specifications tested. If DPI has a secondary packaging, the stability test should be performed both at 25˚C/60% RH (long-term storage) and at 30˚C/65% RH (one-half of the proposed expiration dating period). Description, assay, impurities and degradation products, delivered dose uniformity, aerodynamic particle size distribution, particulate matter, microbial limits, and water or moisture content attributes should be tested during stability studies [30].

The efficacy of DPIs can be enhanced by formulating novel drug delivery systems with an ability to improve aerodynamic parameters, stability of formulations, and physicochemical properties of drugs. Although a clear distinction between various drug delivery systems used as DPIs is difficult, dry powder formulations as polymeric, lipid-based, microparticulate, nanoparticle-based, and cyclodextrin complexes are discussed below.

2. POLYMERIC DRY POWDER INHALERS

To obtain sustained drug release and protection against enzymatic degradation of active substances, polymers are frequently utilized to produce DPIs [31] (Table 1). Polymeric DPIs were primarily developed to modify the rapid drug release properties of water-soluble formulations. Biocompatible polymers such as polyvinyl alcohol (PVA) and poly (lactic-co-glycolic acid) (PLGA) are often used as sustained drug release agents owing to their low toxicity [32-34]. Polylactide (PLA), poly-caprolactone (PCL), hydroxyl propyl methyl cellulose (HPMC), chitosan, gelatin, hyaluronic acid (HA), Locust Bean Gum (LBG) are some other polymers used to produce polymeric dry powder inhalers [35]. However, prolonged exposure of the lungs to increased amount of polymer, required to reach the desired drug concentration in the target region, may trigger pulmonary inflammation and/or fibrosis [36, 37]. To overcome this problem, natural polymers are increasingly being used instead of synthetic polymers [38-40]. Moreover, powder drug formulations based on nanoparticles are more stable than those based on liposomes and protect the active substance from airway defense mechanisms, such as mucociliary clearance and phagocytosis [41]. However, toxicity associated with inhalable nanoparticles remains a concern that needs to be addressed.

Andrade et al. used thin-film hydration and freeze-drying techniques to produce and evaluate insulin-containing self-assembled polymeric micelles as DPIs. The Andersen Cascade Impactor was used at a flow rate of 28.3 L/min and 4 L of airpass condition to evaluate *in vitro* aerosolization and deposition properties of these particles. Using a rotahaler, the study reported FPF higher than 44% and MMAD less than 5.1 μm [42].

Rezazadeh et al. produced paclitaxel containing polymeric micelles as DPI using spray drying technique. In this study, systemic side effects are expected to be alleviated by local application. Tocopheryl succinate and polyethylene glycol were used to produce polymeric micelles. Aerodynamic parameters of obtained DPI were evaluated using Andersen Cascade Impactor with Spinhaler® device. MMAD, FPF and emitted dose (%) were <4 μm, 60.1±10.23% and 89.8±4%, respectively [43].

Polymeric dry powder inhalers can be produced in many different ways. For instance, Farhangi et al. developed ciprofloxacin-loaded polymeric nanomicelles by spray drying process using chitosan-lipid conjugates. Produced formulations had significantly higher antibacterial effect compared to free ciprofloxacin. Volume mean diameter and FPF of the formulation were 1.7 μm and 60%, respectively [44]. As can be seen from the examples given, it is possible to obtain DPI with different aerodynamic properties by changing the production parameters.

Table 1. Examples of polymeric DPIs along with key results.

System Type	Drug	Results	Ref.
Polymeric DPIs	Budesonide	FPF: 52.8 ± 1.0%, MMAD: 2.21–5.75 μm	[45]
Large porous polymeric DPIs	Deslorelin	Plasma concentration of deslorelin in the large-porous DPI analysis was 120-fold higher compared to untreated deslorelin. Plasma concentration of deslorelin in the large-porous DPI analysis was 2.5-fold higher compared to small conventional DPI.	[46]
Large porous polymeric DPIs	Doxorubicin	Diameter: 14.1 ± 2.1 μm, MMAD: 3.6 ± 0.4 μm	[47]
Cyclodextrin containing large porous polymeric DPIs	Insulin	Density: 0.144 ± 0.007 g/mL, MMAD: ~10 μm	[48]

3. LIPID-BASED DRY POWDER INHALERS

3.1. Liposomes

Liposomes are vesicles that can act as potential drug-delivery systems. However, their use is limited owing to their poor stability. To circumvent this problem, solid liposomes also called lipospheres or pro-liposomes are developed. Pro-liposomes refer to granular products containing the dry powder and phospholipid precursors that can form liposomes on hydration before or after drug administration [49, 50]. Liposomes are biologically compatible, biodegradable, and non-toxic structures as these are prepared from phospholipids present in the pulmonary surfactant. Liposomes can carry both hydrophilic and lipophilic drugs. Moreover, these can efficiently and systemically deliver cytotoxic, anti-asthmatic, anti-microbial, and

anti-viral active substances. The selected excipients used in pro-liposome production are known to affect not only the drug release profile but also the aerosolization performance [51, 52] (Table 2). For example, Li et al. developed liposomal andrographolide DPIs using the injection method to treat bacterial pneumonia and obtained 4.87 µm MMAD and 23.03% FPF [53].

Chennakesavulu et al. developed colchicine and budesonide containing liposomal DPIs for treatment of idiopathic pulmonary fibrosis. Thin layer film hydration method was used to obtain liposomes with average size below 100 nm. Produced liposomes were freeze dried with mannitol to acquire dry powder formulation and evaluated using Andersen Cascade Impactor. FPF and MMAD values were 45-50% and <5 µm, respectively [54]. As a result, it is seen that liposomal formulations can be obtained with different aerodynamic properties.

3.2. Solid lipid nanoparticles

An alternative system to classical colloidal systems, such as emulsions and liposomes, is solid lipid nanoparticle (SLN). Large-scale production of SLNs is possible and these could easily be loaded with several active substances (e.g., prednisolone, diazepam, and camptothecin) [55] (Table 2).

Rosière et al. developed chitosan derivative-coated SLNs containing paclitaxel to target lung cancer cells. Nanoprecipitation and spray drying methods were utilized to obtain these nanoparticles. *In vitro* aerosolization characteristics were assessed using a Multi-Stage Liquid Impinger, Axahaler® and size 3 hydroxypropyl methylcellulose (HPMC) capsule filled with 20 mg powder (100 L/min for 2.4 seconds). Moreover, *in vitro* cell viability assay, performed using the human ovarian HeLa cell line, revealed increased anti-cancer activity compared with that of commercially available paclitaxel formulation (Taxol) along with 34% FPF [56].

Bakhtiary et al. produced DPIs containing erlotinib-loaded SLNs for treatment of non-small cell lung cancer. After obtaining <100 nm SLNs, spray drying method was used to produce DPIs without and with mannitol. Aerodynamic parameters were tested using Next Generation Impactor. The emitted dose (%), FPF (%), MMAD, geometric standard deviation were 87.16±0.16%, 24.25±0.72%, 5.528±0.47 µm, 2.582±0.06 µm for without mannitol DPI, 94.91±0.15%, 30.98±0.87%, 3.931±0.31 µm, 4.339±0.07 µm for with mannitol DPI, respectively [57]. As it is understood from the data, excipients such as carriers, cryoprotectants used in the production stage can improve the aerodynamic properties of DPIs.

3.3. Solid lipid microparticles

Solid lipid microparticles (SLMs) are one of the DPI formulation approaches that provides controlled drug release. SLMs are similar to oil in water (o/w) emulsions; however, oils with a high molecular weight and that are solid at room temperature are used. The hydrophobic active substance is entrapped inside the oil droplet and the microparticles are stabilized with a surfactant. The drug is dissolved in the melted oil, and subsequently, the resulting solution is mixed with the aqueous phase and homogenized to reduce the droplet size. When the desired droplet size is obtained, the system is cooled to produce SLMs using methods such as drying or filtration [58] (Table 2).

Scalia et al. produced quercetin-containing microparticles by o/w emulsification method using the phase inversion technique. For this, tristearin was used as the lipid component and phosphatidylcholine as an emulsifier. Although formulation with an aerodynamic diameter of less than 5 µm was obtained, the FPF value was calculated to be 20.5 ± 3.3% with the Next-Generation Impactor [59]. This suggests the importance of considering the emitted dose when evaluating the FPF parameter.

Maretti et al. developed SLMs containing rifampicin to target alveolar macrophages for treatment of tuberculosis. Apparent density, bulk density, tapped density and porosity were 1.058±0.010 g/cm^3, 0.070±0.002 g/cm^3, 0.161±0.020 g/cm^3, 80.44±0.05%, respectively. Although volume mean particle size of SLM was 1.15±0.25 µm, calculated aerodynamic diameter was 0.51±0.08 µm [60]. As a result, when the porosity of the particles increases and therefore the density decreases, the aerodynamic diameter appears to be smaller than the volume diameter.

3.4. Nanostructured lipid carriers

Nanostructured lipid carriers consist of a solid lipid core and a surfactant to stabilize this core. Both lipophilic and hydrophilic drugs could be delivered using this system. Some of the advantages of this system include biocompatibility, biodegradability, high drug loading capacity, controlled drug release ability, long-term stability, and the possibility of scaling-up [61] (Table 2).

Patil-Gadhe et al. developed rosuvastatin-loaded nanostructured lipid carriers without or with L-leucin as DPIs using melt-emulsification, ultrasonication, and lyophilization methods. The aerosolization parameters were examined at 30 L/min and 60 L/min flow rates using Westech 8 stage non-viable Cascade Impactor. In the presence of leucine, aerodynamic parameters were shown to improve. It was shown that MMAD and geometric standard deviation (GSD) decreased and FPF increased when the flow rate was increased from 30 L/min to 60 L/min. *In vitro* aerosolization tests yielded <3 µm MMAD and >90% FPF at a flow rate of 60 L/min [62]. As can be seen from the data, the inhalation rate can change the aerodynamic parameters independently of the formulations.

Table 2. Examples of lipid-based DPIs along with key results.

System Type	Drug	Results	Ref.
Solid lipid microparticles	Budesonide	Volume diameter: 3.0–3.5 µm, FPF: 21.1 ± 0.6 - 29.5 ± 0.3%	[58]
Solid lipid microparticles	Salbutamol acetonide	True density: 0.752 ± 0.013, 45% of SLMs have a volume diameter of 0.5 – 6 µm	[66]
Solid lipid microparticles	Rifampicin	Volume diameter: 1.15 ± 0.25–1.16 ± 0.33 µm, aerodynamic diameter: 0.51 ± 0.08 µm	[60]
Solid lipid microparticles	Compritol	Volume diameter: 4.1 ± 1.1 - 12.9 ± 0.9 µm	[67]
Liposomal	Tacrolimus	FPF: 71.1 ± 2.5%, MMAD: 2.2 ± 0.1 µm, GSD: 1.7 ± 0.2	[68]
Liposomal	Dapsone	FPF: 75.6 ± 1.6%, MMAD: 2.2 ± 0.1 µm, GSD: 2.3 ± 0.1	[69]
Liposomal	Rifampicin	FPF: 66.8 ± 6.2%, MMAD: 3.4 ± 0.5 µm	[70]
Liposomal	Amikacin	FPF: 29.2 ± 2.1%, Mean size of liposomes: 2.0 ± 0.2 µm, Angle of repose (θ): 28.7 ± 0.5	[71]
Liposomal	Insulin	FPF: 31.40 ± 2.15%, MMAD: 5.07 ± 0.26 µm, bioavailability 38.38%	[72]
Liposomal	Amphotericin B	FPF: 22.6 ± 2.2%	[73]
Liposomal	Budesonide	FPF: 20.69 ± 1.50	[74]
Liposomal	Ciprofloxacin	FPF: 60.6 ± 12.2%, MMAD: 2.8 ± 1.0 µm	[75]
Liposomal	Salbutamol sulfate	FPF: 41.51 ± 2.22%	[76]
Solid lipid nanoparticles	Ethambutol	ED: 94.70 ± 1.09%, FPF: 30.91 ± 0.77%, MMAD: ~4.0–5.5 µm	[77]
Solid lipid nanoparticles	Alendronate	ED: 96.34 ± 0.98%, FPF: 11.87 ± 0.22%, MMAD: ~6.0– 7.0 µm	[78]
Solid lipid nanoparticles	Insulin	MMAD: 2.04 ± 0.17 µm, low bulk density: 0.06146 ± 0.0045 g/cm^3, emitted fraction: 92.54 ± 0.77%, respirable fraction: 66.89 ± 3.02%	[79]
Nanostructured Lipid Carriers	Montelukast	Particle size: 184.6 ± 2.7 nm, ED: 95%, MMAD: 2.83 ± 0.46 µm, FPF: 90.22 ± 2.6%, 12-fold increase in bioavailability	[23]
Nanostructured Lipid Carriers	Rosuvastatin	MMAD:<3 µm,FPF: >90% at 60 L/min	[62]
Lipid-polymer nanoparticles	Levofloxacin	ED: <68%, fine particle fraction: <23% (w/w), MMAD: 6.8–7.8 µm	[63]
Lipid-polymer nanoparticles	-	ED: ~75%, fine particle fraction: ~25%, loading:~30%	[64]
Lipid-polymer nanoparticles	Isoniazid and ciprofloxacin hydrochloride	ED: ~88%, FPF: ~63%, MMAD: ~2.45 µm	[65]

3.5. Lipid–polymer nanoparticles

Lipid–polymer nanoparticle systems use the properties of nanosystems, polymers, and liposomes to increase bioavailability. These are obtained by coating the polymer nanoparticle core with a lipid layer. The ratio of lipid to polymer is very crucial as it directly affects the encapsulation efficiency and release properties of the active substance. Lipid–polymer nanoparticles-based DPIs frequently use poly (lactic-co-glycolic acid) as the polymer and lecithin as the lipid source. As particles smaller than 1 µm are exhaled, the nanoparticles are transformed into microscale structures (nanoaggregates or nanocomposites having a theoretical aerodynamic diameter between 1 and 5 µm) to achieve effective aerosolization [63-65] (Table 2).

Wang et al. produced levofloxacin-loaded lipid–polymer hybrid nanoparticles using spray drying and spray-freeze-drying methods. Spray-freeze-drying method was found to be superior over spray drying method in terms of aerosolization characteristics because DPI produced using the spray-freeze-drying method had higher ED (max 92%) and FPF (26%) [63]. This shows that the production method can change the aerodynamic parameters and thus treatment efficacy.

Bhardwaj et al. developed isoniazid and ciprofloxacin hydrochloride containing lipid–polymer hybrid nanoparticles using spray drying method for the treatment of tuberculosis. Characterization of DPI was investigated in terms of aerodynamic properties using an eight-stage Andersen Cascade Impactor at 28.3 L/min flow rate for 10 s. When isoniazid loaded DPI and ciprofloxacin hydrochloride loaded DPI results were compared, emitted dose (%), FPF and MMAD values were obtained very close to each other [65]. This shows that the developed DPI production method may be suitable for formulating different active ingredients.

4. MICROPARTICULAR DRY POWDER INHALERS

Microparticles are defined as microcapsules or microsphere systems that are prepared using hydrophilic and lipophilic drugs having a particle size of 1 to 999 µm. However, aerodynamic diameters should be in the range of 1 to 5 µm for microparticles formulated as DPIs. The active substances in the solid, solution, suspension, or emulsion forms can be encapsulated inside the particles. The microparticles can be prepared with the desired size, shape, and porosity by changing the process parameters. Microparticles administered by the pulmonary route to target alveolar macrophages are more efficient in delivering high amounts of the active substance to the cells to treat diseases such as tuberculosis. In the treatment of other diseases, alveolar macrophages should be avoided to prevent pulmonary clearance and thereby increase the alveolar half-life and bioavailability of the active substance. Approaches such as carrier-free microparticles and large porous microparticles can be used to prepare microparticulate DPIs for the intended purpose (Table 3).

4.1. Carrier-free microparticles

To improve the flow and aerosolization properties of micronized drugs, excipients are included in inhaler formulations. However, suitable excipients for inhalation are considerably limited; moreover, the addition of a large amount of excipient to the formulation reduces the amount of active agent in the formulation and only microgram levels of formulation can be used as DPIs. Since addition of a carrier increases the volume of the powder formulation, carriers are usually not combined with drugs administered at high doses (such as antibiotics). Thus, studies have been performed to manufacture formulations that do not require a carrier to improve the flow of the micronized drug. However, some market preparations such as Pulmicort® (budesonide) and Bricanyl® (terbutaline) DPIs have been formulated without carriers even though they contain low amounts of the drug [80] (Table 3).

Akdag Cayli et al. formulated ciprofloxacin hydrochloride and levofloxacin hemihydrate with or without N-acetylcysteine or dornase alpha as carrier-free DPI microparticles using the spray drying method. Although MMAD values of all formulations were between 2 and 3 µm, the highest FPF (85%) was obtained with the levofloxacin hemihydrate and N-acetylcysteine combination DPI [81]. This suggests that DPIs are formulations suitable for combined drug therapy.

Similarly, Yazdi et al. developed carrier-free DPI of ibuprofen using air-jet milling method. Aerosolization properties were investigated using a Next Generation Impactor (HPMC capsule containing 10, 25, or 50 mg ibuprofen). The emitted dose (%), FPF, and MMAD were 69-73%, 72-80%, and 2.6-2.9 µm, respectively [82]. This shows that DPIs can be produced using easy, one-step methods suitable for scale-up and industrial manufacturing.

4.2. Large porous microparticles

As per the aerodynamic diameter formula, aerodynamic diameters of particles with low density are lower than their volume diameters (Eq. 1). Large porous particles are frequently preferred in the production of DPIs owing to their low density. Moreover, their good flow properties are attributed to their large volume diameters, whereas they exhibit good aerosolization owing to their small density (Table 3).

Koushik et al. compared large porous DPIs (mean diameter: 13.8 µm; density: 0.082 g/mL) and small conventional DPIs (mean diameter: 2.2 µm; density, 0.7 g/mL), which contained deslorelin as the active substance and PLGA as the polymer. After 7 days of intratracheal administration of DPIs to Sprague-Dawley rats, plasma concentrations of deslorelin in the large porous DPIs were 120-fold and 2.5-fold higher as compared with the untreated deslorelin and small conventional DPIs, respectively [46]. This data implies that, by reducing the density of DPI; aerodynamic properties can be improved, high amounts of drug can be delivered deep into the lungs and thus, the amount of drug entering the systemic circulation may increase.

Similarly, Kim et al. developed doxorubicin-loaded highly porous large PLGA microparticles as a sustained- release inhalation system. Although the volume diameter was 14.1 ± 2.1 µm, MMAD was 3.6 ± 0.4 µm. Moreover, as expected, the volume diameter was greater than the aerodynamic diameter [47]. This study demonstrates that DPI formulations are also suitable for sustained release. However, it is important to consider the clearance mechanism of the lung in sustained release formulations.

Table 3. Examples of microparticulate DPIs along with key results.

System Type	Drug	Results	Ref.
Carrier-free microparticles	Tobramycin	FPF: 56 ± 1%	[83]
Carrier-free microparticles	Ciprofloxacin, levofloxacin, acetylcysteine, dornase alfa	FPF: 65.82 - 85.18%, MMAD: 2.29–3.20 µm, ED: 53.75–69.18%	[81]
Carrier-free microparticles	Salbutamol sulphate	FPF: 42–47%, MMAD: 1.9–3.7 µm, GSD: 1.2–1.8	[84] [85]
Carrier-free microparticles	Sodium cromoglycate	With carrier-free sodium cromoglycate, significantly fewer inhalations to empty the capsules compared to sodium cromoglicate plus lactose DPIs	[86]
Carrier-free microparticles	Tobramycin	FPF: 50.5–68.3%, MMAD: 1.3–3.2 µm	[87]
Carrier-free microparticles	Budesonide, salbutamol sulphate	FPF: 47–53%, MMAD: 3.0–4.1 µm, GSD: 1.7	[88]
Large porous microparticles	Heparin	entrapment efficiency: 54.82 ± 2.79%, MMAD: 2–6 µm, volume-based mean diameter: 5–11.5 µm	[89]

5. NANOPARTICLE-BASED DRY POWDER INHALERS

Nanoparticle-based DPIs [41] are administered through the pulmonary route. However, nanoparticles of small particle size (10–1000 nm) are not suitable for accumulation in the lungs and get removed from the respiratory tract by exhalation. This problem could be overcome using spray-drying [63, 90, 91] or spray-freeze-drying of nanoparticles with mannitol, PVA, leucine [92, 93], or by co-administering carrier particles, such as lactose [94].

Inhalable nanoparticle formulations are preferred because they improve the solubility of water-insoluble drugs and reduce the mucociliary clearance [31]. In addition to these properties, nanoparticles could be selectively delivered to target sites, especially those targeted against tumors [41, 95].

In addition to polymeric and lipid-based nanoparticles, other DPI preparation approaches such as inorganic nanocarriers, actively targeted inhalable nanoparticles, nanocrystals, nanocomposites, and nanoaggregates are available (Table 4). In this section, nanoparticular systems other than polymeric and lipid-based systems are discussed.

5.1. Inorganic nanocarriers

Inorganic carriers are preferred for producing DPIs, considering their beneficial physicochemical properties. Particularly, silica nanoparticles are commonly used to produce DPIs because of the biocompatible and biodegradable properties of amorphous silica. In addition, silica particles are more stable than organic-based drug delivery systems. The morphology of silica particles can be manipulated, and their surfaces can be decorated [96] (Table 4).

Cheow et al. manufactured hollow spherical aggregates of biocompatible silica nanoparticle by optimizing spray drying method parameters using an experimental design methodology. At low pH and at low feed concentration of spray drying method, small geometric size and aerodynamic size were achieved. They obtained particles with geometric diameter greater than the aerodynamic diameter to ensure uniform particle size distribution and dosing while increasing the aerosolization property [96]. This demonstrate that, by optimizing the parameters in the spray-drying method, which is frequently used in DPI production, hollow particles can be produced, thereby reducing the density and improving the aerodynamic parameters.

5.2. Nanocrystals

Nanocrystal® (Elan Pharmaceutical Technologies, USA) technology is a milling process employed to decrease the particle size to below 400 nm. The ball mill method can be processed as wet mill. Thus, the amorphous regions in the particles undergo recrystallization since the production is carried out in an aqueous medium. This shows that wet milling results in stable moisture-resistant particles with a more uniform crystal structure as compared with that obtained by dry milling. Excipients such as PVP and lecithin are used to provide physical stability to the active substance by preventing the aggregation of nanoparticles. Major disadvantages of the nanocrystalline approach are that the long-term toxicity of excipients in the respiratory system is not completely known and the processing time could be very long [97] (Table 4).

Onoue et al. developed tranilast-containing nanocrystalline solid dispersions to minimize systemic exposure and maximize local pharmacological effect. DPI formulations were produced using combination of wet-milling, freeze-drying and jet milling methods. The dispersibility of produced DPIs were assessed using an eight-stage Andersen Cascade Impactor. The emitted dose and the FPF were 97.9% and 59.4% before storage at room temperature for 9 months, respectively. After the storage, emitted dose was 99.2% and FPF was 53.9%. This study found that in addition to good aerodynamic properties, the pharmacologically effective dose for intratracheal administration was approximately one-fifth of the oral dose [98]. This study demonstrates that produced DPI formulations may have high aerosolization performance after long-term storage.

Hu et al. produced curcumin nanocrystals to develop DPI formulation. For this purpose, they used combination of wet milling and spray drying methods. In this study, the effects of different milling times on aerosolization properties were also evaluated using a Next Generation Impactor. It was shown that as the milling time increases from 10 min to 40 min, FPF increases from 62.4% to 72.3%, and therefore the amount of drug that is expected to reach the deep of the lung increases [99]. As can be seen from the presented data, production parameters can dramatically affect the aerosolization properties of DPI formulations.

5.3. Nanocomposites and nanoaggregates

Nanocomposites are systems in which nanoparticles are brought together using a carrier such as sugar and polymer. Nanoaggregates are obtained by holding large porous or hollow nanoparticles together with physical forces such as van der Waal's force [100]. Nanocomposites and nanoaggregates of DPIs are successfully able to counter mucociliary clearance, macrophage-mediated phagocytosis, and enzymatic degradation without any exhalation problems [101] (Table 4).

Yamamoto et al. produced PLGA nanocomposite to develop insulin-containing DPI. For this purpose, after emulsion solvent diffusion method, spray-drying fluidized bed granulation method was used. A cascade impactor was performed to measure inhalation properties of produced DPIs at 28.3 L/min for 5 s using Spinhaler® and Jethaler® devices. In studies conducted with Jethaler®, respirable fraction (aerodynamic diameter below 7 µm) of DPIs was higher than studies with Spinhaler® [102]. As this study demonstrates, the use of different devices can change aerodynamic parameters independent of formulation and inhalation parameters.

Kaur et al. used spray drying method to produce DPI formulation from isoniazid and rifampicin nanoaggregates and obtained an aerodynamic diameter of less than 4 µm for both isoniazid and rifampicin containing DPIs [103]. Thus, it was shown that different active substances can be produced as DPI formulation by the same production method.

Table 4. Examples of nanoparticle-based DPIs along with key results (except polymeric and lipid-based DPIs).

System Type	Drug	Results	Ref.
Inorganic nanocarriers	Silica (inorganic compound)	Particle mean aerodynamic diameter: 1.5–3.0 µm, hollow spherical aggregates	[96]
Nanoaggregate	Isoniazid and rifampicin	Drug encapsulation efficiency: 60%–70%, aerodynamic diameter of isoniazid: 2.74 µm, aerodynamic diameter of rifampicin: 3.82 µm, particle size of nanoparticles: 450–865 nm	[103]
Nanocrystal	Cinaciguat	Mean volume diameter (Dv50): 3–4 µm, experimental MMAD: 4–4.5 µm, FPF: 40–45%, ED: 94–95%	[104]
Nanocrystal	Celecoxib	MMAD: 4.82 ± 0.21 µm, FPF: 31.93 ± 3.93%, GSD: 1.81 ± 0.05	[105]
Nanocrystal	Budesonide	Mean volume diameter of budesonide: ~260 nm, ED: 94.9 ± 1.0%, FPF: 35.6 ± 3.3%, MMAD: 5.33 ± 0.05 µm, GSD: 1.68 ± 0.02	[106]
Nanocrystalline solid dispersion	Tranilast	ED: 98%, FPF: 60%, mean diameter of tranilast: 122 nm	[98]

6. CYCLODEXTRIN COMPLEX

Cyclodextrins (CD) are cyclic oligosaccharides, outer part of which carries the hydroxyl groups and is hydrophilic and the inner space is lipophilic. The active substances are bound to CDs by forming an inclusion complex. One of the widely used CDs in the pharmaceutical industry is β-CD, owing to the size of the cavity, complexing activity, and cost-effectiveness [107]. CDs protect the active substance from enzymatic degradation and provide a sustained release, thereby increasing the bioavailability of the drug and allowing the desired release profiles to be obtained [108] (Table 5).

Table 5. Examples of cyclodextrin complex DPIs along with key results.

System Type	Drug	Results	Ref.
Cyclodextrin containing large porous polymeric DPIs	insulin	density: 0.144 ± 0.007 g/mL, MMAD: ~10 µm	[48]
Cyclodextrin complex	Beclomethasone diproprionate	Emitted fraction: 81.9% ± 3.2	[111]
Cyclodextrin complex	Budesonide	ED: 68.0% (RSD: ± 26.1%), FPF: 67.7% (RSD: ± 18.9%)	[112]
Cyclodextrin complex	Fisetin	ED: 97.31 ± 0.74, FPF: 75.83 ± 3.34%, FPD: 7.06 ± 0.30 mg, MMAD: 2.0–2.5 µm	[109]

Mohtar et al. produced dry powder CD complexes for pulmonary delivery of fisetin using three different kind of CDs by spray drying method in the presence of ethanol, and obtained 97.31 ± 0.74% ED, 75.83 ± 3.34% FPF, 7.06 ± 0.30 mg FPD, and 2.0 to 2.5 µm MMAD values, all indicators of their effective aerodynamic behavior. The use of ethanol in the spray-drying step increased FPF 2-fold, while leucine in the formulation increased FPF 2.3-fold [109]. The given data show that the excipients used in the spray-drying step or formulation may alter the amount of drug reaching the deep of the lung.

Kinnarinen et al. developed budesonide/γ-cyclodextrin complex as DPI by dry mixing method. Lactose was used as a carrier. Aerosolization properties were tested before and after 1 month storage at 40˚C, 75% RH conditions using an Andersen Cascade Impactor. Respirable fraction of budesonide/γ-cyclodextrin complex was 35% before storage, 31% after storage [110]. As shown in the present study, aerodynamic properties may

change during storage. Therefore, testing the aerodynamic parameters during shelf life and demonstrating that they are at the desired level is very important in terms of achieving uniform treatment.

7. CONCLUSIONS

DPIs are considered promising drug-delivery systems in the healthcare industry; however, challenges faced in obtaining a reproducible therapeutic and non-toxic effect limit the use of these inhalers. Nevertheless, with the rapid improvement in production technologies and test methods, a tremendous increase has been observed in the use of inhalers. Pulmonary administration is still one of the most effective methods for achieving both local and rapid systemic effects. As DPIs are also the most stable formulations that can be administered via inhalation, the scientific community is currently focusing on improving the available formulations, including overcoming the associated drawbacks.

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