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The future of dry powder inhaled therapy: Promising or discouraging for systemic disorders?

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ABSTRACT

Dry powder inhalation therapy has been shown to be an effective method for treating respiratory diseases like asthma, Chronic Obstructive Pulmonary Diseases and Cystic Fibrosis. It has also been widely accepted and used in clinical practices. Such success has led to great interest in inhaled therapy on treating systemic diseases in the past two decades. The current coronavirus (COVID-19) pandemic also has increased such interest and is triggering more potential applications of dry powder inhalation therapy in vaccines and antivirus drugs. Would the inhaled dry powder therapy on systemic disorders be as encouraging as expected? This paper reviews the marketed and in-development dry powder inhaler (DPI) products on the treatment of systemic diseases, their status in clinical trials, as well as the potential for COVID-19 treatment. The advancements and unmet problems on DPI systems are also summarized. With countless attempts behind and more challenges ahead, it is believed that the dry powder inhaled therapy for the treatment of systemic disorders still holds great potential and promise.

1. Introduction

1.1. Pulmonary drug delivery

Pulmonary drug delivery, the intake of medication through oral inhalation to the lungs is drawing more attention as a promising alternative to traditional drug delivery systems. In 2016, the global market of inhaled products reached $36.10 billion with an exceptional compound annual growth rate of 6.5% to grow to $52.37 billion by 2021 (Pulmonary/ Respiratory Drug Delivery Market by Formulation, Device Type, Canister, End User, Applications - Forecasts to, 2021). Pulmonary drug delivery, also referred as orally inhaled therapy, has been shown to be attractive and effective in treating local lung diseases like asthma, Chronic Obstructive Pulmonary Diseases (COPD) and cystic fibrosis (CF) in active pharmaceutical ingredients (APIs) to be directly delivered to lungs, resulting in an immediate response (Zhou et al., 2015; Blasi et al., 2018). Additionally, inhaled therapy has demonstrated great potential for the treatments of systemic diseases, such as diabetes mellitus, Parkinson's disease and schizophrenia (Ledet et al., 2015; Hauser et al., 2019; Pacciardi et al., 2019). This is particularly efficient for delivering APIs which are easily metabolized through oral administration, such as amino acids, proteins, vaccines and other small chemicals, which can directly deposit in deep lungs for quick absorption into the systemic circulation (Shoyele and Slowey, 2006; LiCalsi et al., 1999; Wang et al., 2020).

The respiratory system primarily consists of conducting channels (nose, mouth, pharynx, larynx, trachea, bronchi, bronchioles, terminal bronchioles) and respiratory areas (respiratory bronchioles, alveolar ducts, alveoli) (Groneberg et al., 2003; Liu et al., 2020). Inhalable particles that are small enough in size can pass through such airway systems and deposit in the respiratory areas to undergo dissolution and absorption for further local or systemic efficacy.

Compared with oral administration, pulmonary drug delivery has a number of inherent advantages. It can avoid the first-pass metabolism, allowing the medication to be delivered directly to the lungs, thus reducing the chance of gastrointestinal adverse reactions (Komase et al., 2014; Geller et al., 2011). This also maintains the activity of therapeutics as they will not be affected by the pH level and food in the gastrointestinal tract. Direct delivery to lungs also permits a more rapid absorption of APIs into the bloodstream, due to the large area of air sacs (~100 m^2) with only a thin (0.1–0.2 μm) and highly vascular epithelial layer, which results in faster onsite of action (Laube et al., 2011;

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Rangaraj et al., 2019; Kaur et al., 2014). Furthermore, pulmonary drug delivery provides a needle-free method for patients who suffer from trypanophobia.

1.2. Dry powder formulation and inhaler device

The delivery of drugs directly to the lung, is typically achieved by an aerosol (a suspension of small liquid droplet or fine solid particle dispersed in gas medium), in the form of a spray (Tellier et al., 2019). Nebulizer, pressurized metered-dose inhaler (pMDI), and DPI are the three primary technologies used to form sprays for pulmonary drug delivery (Srinivasan and Shetty, 2017). First introduced during the 19th century, the nebulizer is a device that delivers the liquid medication to lungs in the form of mist. Although it has been practiced in various traditional medicines over centuries, it is now globally adopted as pre-hospital and in-hospital emergency care of acute disorders or long-term treatment of chronic diseases (Stein and Thiel, 2017; Chinese College of Emergency Physicians (CCEP), 2019). The nebulizer is however relatively large, has a long aerosolization time, and requires dismantling and cleaning after each use. pMDI is a device that sprays liquified propellant-drug suspension/solution to form small droplets in a short burst for lung delivery. It first appeared on the market in the mid-1950s. Due to its high level of delivery consistency and cost effectiveness, it is commonly used for treating respiratory diseases and has taken a great market share. Most patients can not however, use it properly, as pMDI requires high coordination between actuation and inhalation. Additionally, environmental concerns resulting from the gas propellant drive the replacement of pMDI (Smith and Parry-Billings, 2003). As an alternative, DPI delivers medication to the lungs in the form of fine powder. Although it emerged as a latecomer in 1967, DPI has received more attention and preference nowadays for several reasons (Lin et al., 2015): The solid state of DPI formulation is more stable than the liquid form of the nebulizer and pMDI (Srinivasan and Shetty, 2017; Shur et al., 2015). The elimination of propellants, chlorofluorocarbon (CFCs) or hydrofluoroalkanes (HFAs), avoids ozone depletion and greenhouse issues (Devrim et al., 2011). The ease of use and capability of high-dose delivery causes DPIs to be more widely adopted. In addition, coordination between the inhalation of patients and actuation of device is not necessarily required due to the breath activation mechanism of most DPIs (Muralidharan et al., 2015). Those breath activated DPIs, however, require a forceful inhalation to fluidize the drug powders and generate suitable pharmaceutical aerosols. Although most patients can achieve this, it may be challenging for children and patients with severe lung impairments to generate a sufficient inspiratory airflow (Lavorini et al., 2017).

The DPI product is a combination of drug formulation and an inhaler device. DPI drug formulation contains drug particles suitable for inhalation with an aerodynamic diameter of 1–5 μm, which is universally believed to be able to reach and deposit in the deep lungs (Yang et al., 2014). In most cases, two strategies for DPI formulation are used: 1) carrier-free formulation which contains solely micronized particles; and 2) carrier-based formulation where micronized drug powders blend with coarse carrier particles (drug-carrier mixture). Carrier-free formulation containing only fine drug particles are generally highly cohesive and tend to form aggregates, leading to poor flowability, insufficient dispersion, and low dose uniformity (Kinnunen et al., 2014). Carrier-based formulation uses large lactose as carriers to improve flowability for easy handling, dispensing and metering of the drug. Coarse lactose, mostly α–monohydrate lactose, acts as host particles to blend with these fine drug particles in order to form an ordered mixture that helps improve bulk property (Pilcer et al., 2012; Hassoun et al., 2015; Hoppentocht et al., 2014). While having improved flowability, the fine drug particles being carried on the surface of coarse lactose, may not be completely separated out during inhalation, thereby reducing fine particle lung deposition.

The dry powder inhaler devices are generally categorized into single-unit dose inhalers, multi-unit dose inhalers and multidose reservoir-inhalers by the number of doses, as shown in Fig. 1 (Zhang et al., 2012). The single-unit dose inhalers which are mostly capsule-based, are usually pre-metered, though patients have to load the hard capsule containing drug formulation before each use (Fig. 1A). Multi-unit dose inhalers, which are usually blister-, disk-, cartridge-based devices, deliver individual dose from pre-metered unit (Fig. 1B) (Berkenfeld et al., 2015). As for the reservoir device, the drug particles, often engineered particles for an easier flow, is sealed into the reservoir as one dose is metered from the bulk by the built-in metering mechanism with each actuation (Fig. 1C). The typical airflow pathways for the three different types of inhalers are shown in Fig. 1 by the arrowed lines. The DPIs may be either breath-activated device (passive device) or power-driven device (active device) based on the dispersion mechanism (Chandel et al., 2019). Most of the currently available DPIs are passive devices, which solely depends on patient inspiratory flow to aerosolize drug powders, alleviating the coordination issue for the pMDI (Kaur et al., 2014). The active devices have also been advanced in recent years through the addition of external energy sources, such as compressed air and piezoelectricity to aerosolize medication with high dose consistency, making it especially suitable for patients with limited lung function (Chan et al., 2014).

The key processes in delivering pharmaceuticals to the lungs using DPIs include powder fluidization, de-attachment of active drug particles from large carriers and/or de-agglomeration from drug-only aggregates, dispersion and transportation of powders, and deposition of drug particles onto the desired sites (Islam and Cleary, 2012). To generate the aerosols, the particle mixture has to be “mobilized” first by the patients’ inspiratory flow through passive inhalers or by external energy through active inhalers. Take the passive inhaler as an example, when patient activates the DPI and inhales, the air is introduced into the powder bed and the static powder blend is fluidized and entrained into the patient’s airways (Lee et al., 2009). Subsequently, the finer drug particles are separated from the carriers or disintegrated from aggregates by forces generated by collisions and turbulent flow, which then go into the lower airways with the airflow while the larger drug particles and agglomerates impact and deposit in the upper conducting areas, especially oropharynx (Daniher and Zhu, 2008). For the carrier-based formulation, it is important that the interactive forces between drug particles and carriers should be strong enough to ensure homogeneity and stability during powder handling, but sufficiently weak to allow the formulation to be readily dispersed for higher lung deposition (Peng et al., 2016). These are realized in the manufacturing process, which is highly correlated with the quality of the final DPI products. To assure the safety, effectiveness, reproducibility and robustness of the final products, the quality by design (QbD) approach is a great necessity, providing not only the guideline but also an understanding of the ultimate scope for DPI development (Ding et al., 2021; Buttini et al., 2018).

1.3. DPI products for local lung diseases

It has been several decades since the dry powder inhalation for diseases treatment had proven its effectiveness in lung diseases, especially asthma and COPD. The main goals of inhalation therapy are the relief of symptoms from the target organ, the maintenance of lung function, and the prevention or eradication of inflammation and constriction (Borghardt et al., 2018). Typically, the most commonly used inhaled drugs for asthma and COPD treatment are corticosteroids, β-adrenergic agonist, and muscarinic antagonist (Currie and Lipworth, 2016; Domingo, 2013). Their functions and typical drugs are shown in Table 1. The medications may be prescribed as a single drug formulation, dual-combination formulation or triple-combination formulation. Out of the dozens of marketed DPI products so far, some FDA (U.S. Food and Drug Administration)-approved key DPI products, which are still commercially available in the market now, are listed in Table 2.

From Table 2, one can see that most of the products are focused on

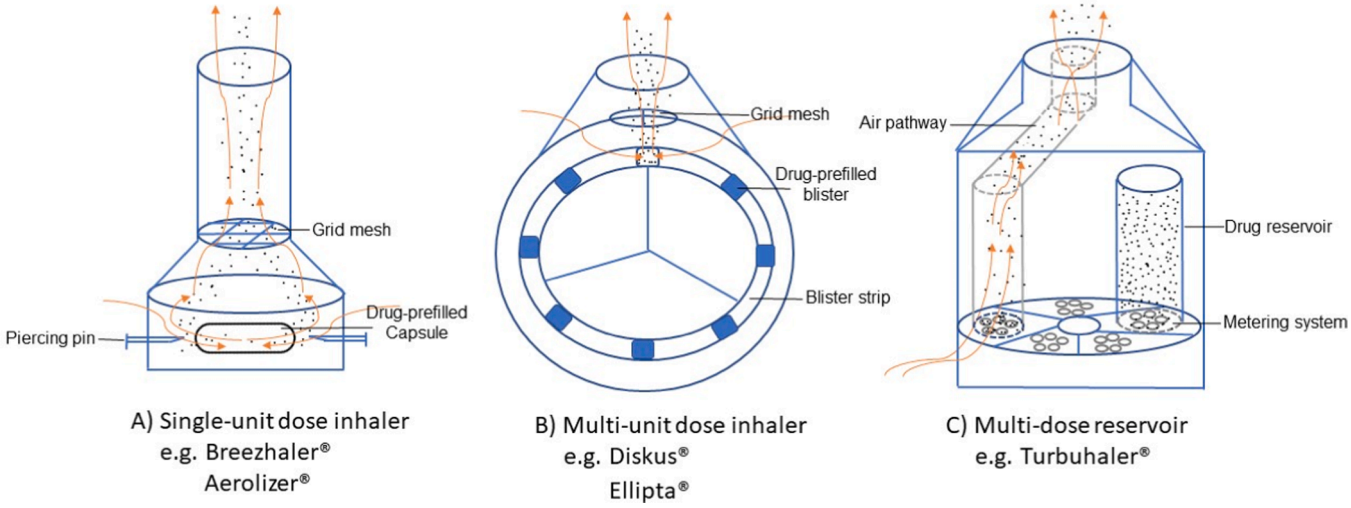

Fig. 1. Types of dry powder inhalers (airflow shown in the arrowed streamlines, drug powder mixture shown as dots).

Table 1
Categories, functions and examples of medications used for asthma and COPD treatments.

Medication categories	Function	Typical drugs
Corticosteroids	Anti-inflammation	Fluticasone Mometasone Budesonide
LABA (Long-acting β-adrenergic agonist)	Bronchioles dilation	Salmeterol Vilanterol Formoterol Indacaterol Olodaterol
SABA (Long-acting β-adrenergic agonist)	Bronchioles dilation	Albuterol Metaproterenol
LAMA (Long-acting muscarinic antagonist)	Bronchioles dilation	Tiotropium Glycopyrronium Umeclidinium Aclidinium
SAMA (Short-acting muscarinic antagonist)	Bronchioles dilation	Ipratropium

treating local respiratory diseases, asthma and COPD, with anti-inflammatories and airway-dilators being the main form of medications. The dry powder formulation is relatively simple and most of the formulations use an API-lactose mixture. The devices used to generate aerosols are passive-dominant, but vary in blister-, capsule- or reservoir-based types with different design complexities. Additionally, following the development history of DPIs, the inhaled dry powder formulation appears to be evolving from a single-drug formulation to double or even triple combination treatment with increased formulation complexity. Meanwhile, generic drugs, such as Wixela® Inhub®, with their price reduced and function enhanced, is gradually emerging on the market, given that more and more product-related patents expired in the past several years. Concurrently, the design of devices has also evolved towards becoming more convenience and digitalized with better aerosolization performance such as Digihaler®.

While inhaled dry powder therapy has long been developed and used in clinical practices for the treatment of respiratory diseases, the advent of inhaled therapy for treating systemic diseases is also gaining popularity and showing promising advancements in the field. As such, a comprehensive review on the products being marketed and in development for systemic disorders is provided in this paper.

2. DPI products for systemic diseases

The target sites for topical respiratory disease treatment by pulmonary drug delivery are mainly located throughout the airways of lungs, especially in the bronchioles region, and drug particles are ideally deposited in the lesion where diseases happen. For the systemic effect, however, the drug particles are expected to settle in the respiratory areas of deep lungs, especially in the alveolar regions, followed by quick transportation across the membrane and being circulated throughout the bloodstream. The detailed delivery process is shown in Fig. 2. Therefore, the design objectives, working principles of inhalation devices and powder formulation for systemic treatment may be different from those on the markets for respiratory diseases. The requirements have become more stringent because more factors related to drug deposition in air sacs, permeation and transportation across the membranes have to be considered when making formulation for systemic disease treatment.

Using dry powder delivery for systemic disorder treatment has been gaining more attention ever since the first product, Exubera®, hitting the market in 2006. Table 3 lists the basic information of the marketed and potential future DPI products for systemic disorders, including diabetes, Parkinson's disease, schizophrenia, headache, and the current COVID-19 pandemic disease. Some of the most important ones are further reviewed in Sections 2.1~2.5.

2.1. Diabetes mellitus

The high number of patients with Diabetes mellitus has continued to grow at an alarming rate across the world with every passing year, fueled by the increasing number of obese and unhealthy individuals (Nilsen et al., 2011). Although insulin is a standard of care for type-I diabetes and a recommendation of care for type-II diabetes, patients have substantial resistance to insulin therapy by subcutaneous injection (Heinemann and Parkin, 2018). Due to the resistance from patients, inhaled insulin therapy is an alternative to traditional blood sugar control strategies, as it reduces the gastrointestinal adverse effects and improving patient compliance by avoiding pains and fears from insulin injections, such as insulin pens, insulin pumps, and insulin syringes.

The earliest and boldest attempt at inhaled therapy for systemic disease treatment came in the form of Exubera®, developed by Pfizer in collaboration with Nektar Therapy, a supposedly blockbuster when it first hit the market in 2006 (Heinemann, 2008). The Exubera® formulation contained an insulin-excipient (mannitol, glycine, sodium citrate dihydrate, sodium hydroxide) mixture packaged in a unit dose blister, which is aerosolized into an extended chamber by an active Exubera® inhaler with compressed air released from a canister in the base of the device and then inhaled by the patient, as shown in Fig. 3 (A) (White

Table 2
Some of FDA-approved DPI products.

Brand name	Drug	Excipients	Indication	Device type	Approval year
Proair® Respiclick®	Albuterol sulfate	Lactose	Bronchospasm	Passive, multidose, reservoir-based	2015
Advair® Diskus®	Fluticasone propionate, Salmeterol xinafoate	Lactose	Asthma/ COPD	Passive, multidose, blister-based	2000
Flovent® Diskus®	Fluticasone propionate	Lactose	Asthma	Passive, multidose, blister-based	1994
Anoro® Ellipta®	Umeclidinium bromide, vilanterol trifenatate	Lactose, MgSt	COPD	Passive, multidose, blister-based	2013
Arnuity® Ellipta®	Fluticasone furoate	Lactose	Asthma	Passive, multidose, blister-based	2014
Bero® Ellipta®	Fluticasone furoate, vilanterol trifenatate	Lactose, MgSt[1]	COPD	Passive, multidose, blister-based	2013
Incruse® Ellipta®	Umeclidinium bromide	Lactose, MgSt	COPD	Passive, multidose, blister-based	2014
Trelegy® Ellipta®	Fluticasone furoate, Umeclidinium bromide, vilanterol trifenatate	Lactose, MgSt	COPD	Passive, multidose, blister-based	2017
Tobi® Podhaler®	Tobramycin	DSPC[2], calcium chloride, sulfuric acid	CF	Passive, single-unit capsule-based	2013
Relenza® Diskhaler®	Zanamivir	Lactose	Influenza	Passive, multidose, blister-based	1999
Airduo® Digihaler®	Fluticasone propionate; Salmeterol Xinafoate	Lactose	Asthma	Passive, multidose, reservoir-based	2017
Armonair® Digihaler®	Fluticasone propionate	Lactose	Asthma	Passive, multidose, reservoir-based	2017
Wixela® Inhub®	Fluticasone propionate, Salmeterol xinafoate	Lactose	Asthma/ COPD	Passive, multidose, blister-based	2019

[1] MgSt: Magnesium Stearate;
[2] DSPC: 1,2-distearoyl-*sn*-glycero-3-phosphocholine.

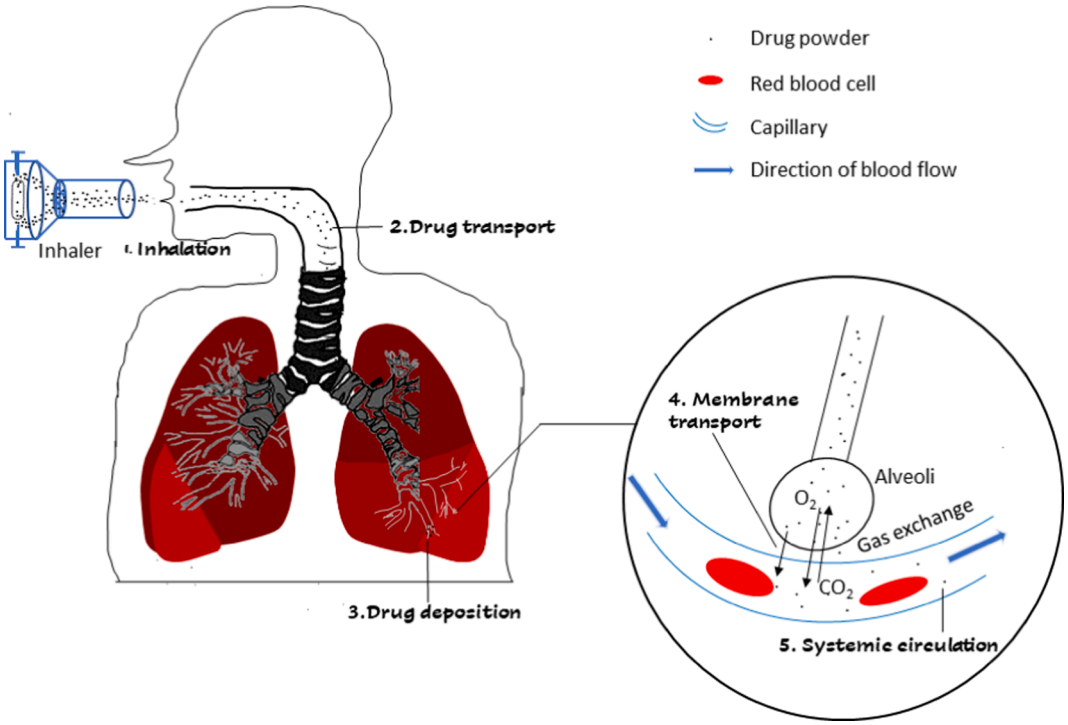

Fig. 2. Dry powder pulmonary drug delivery for systemic diseases treatment.

et al., 2005). In 2007, however, Exubera® was withdrawn due to a number of issues. Such issues behind the withdrawal included being: (1) bulky and large size; (2) inconvenient use of the inhaler; (3) indiscrete and difficult usage for elderly patients, especially the practice of inserting blisters into a small slot and performing all the other necessary steps before inhalation; (4) high price and often no reimbursement options, especially in Europe; (5) relatively low bioavailability/biopotency at 10%-20%, meaning much higher dosage required to achieve the same therapeutic effect as intravenous route; (6) competition coming from the other approved insulin products; (7) safety concerns that a potential lung cancer risk of patients treated with Exubera®, although the FDA noted there was too few cases to confirm if the lung cancer was related to Exubera® (Stein and Thiel, 2017; Heinemann, 2008; Easa et al., 2019).

Influenced by the failure of Exubera®, Eli Lilly and Alkermes Inc,

Table 3
Marketed and future possible DPI products for systemic disorders.

Product	Exubera®	AIR® insulin	Afrezza®	Inbrija®	Adasuve®	Levadex®	CVT427	Possible DPI product
Indication	diabetes	diabetes	diabetes	Parkinson's disease	schizophrenia	migraine	migraine	COVID-19
API	Insulin	Insulin	Insulin	Levodopa	Loxapine	dihydroergotamine	Zolmitriptan	Remdesivir; vaccine antibody
Strength (mg)	1, 3	1, 2.6	0.35, 0.70, 1.0	4	25, 10	–	–	–
Excipients	Sodium citrate, mannitol, glycine, sodium hydroxide	DPPC[1], sodium citrate	Fumaryl diketopiperazine	DPPC, sodium chloride, calcium chloride	None	–	–	–
Device	Active, single-unit, blister-based	Passive, single-unit, capsule-based	Passive, single-use, cartridge-based	Passive, single-unit, capsule-based	Active, single-use, disposable	–	–	–
Market year and FDA status	2006 but withdrawn in 2007	2007, withdrawn pre-market	2014	2018	2012	In-developing	In-developing	In-developing
Companies involved	Nektar and Pfizer	Eli Lilly and Alkermes Inc.	MannKind and Sanofi	Acorda Therapeutics	Alexza Pharmaceuticals	MAP Pharmaceuticals	Acorda Therapeutics	University of Texas; ISR[2] and Conovo
REMS	No	–	Yes	No	Yes	–	–	–
Price in US	–	–	$379 per 90 units	$960 per 90 units	$792 per 5 units	–	–	–

[1] DPPC represents 1,2 dipalmitoyl-*sn*-glycero-3-phosphocholine;
[2] ISR represents Immune System Regulation.

discontinued the development of their inhaled insulin product, AIR® insulin system, a mere five months after the abandonment of Exubera® in 2007, even though clinical studies on diabetic patients had showed favorable efficacy and safety (Ellis et al., 2007). Considered to be a more suitable device and formulation, the AIR® insulin dry powder formulation was packed in capsules and delivered via a small breath-activated Air® inhaler. The insulin particles engineered are with natural lung surfactant (DPPC) and sodium citrate, have a relatively large particle size (>5 μm) but are of low density, allowing for efficient delivery into the deep lungs (Muchmore et al., 2007). Despite the product showing satisfactory aerosolization performances, efficacy and safety, and having passed phase III clinical trials, Eli Lilly still decided to terminate its development after considering that the commercial potential of AIR® insulin was not strong given the safety deficiencies and financial loss of Exubera® demonstrated (Ledet et al., 2015; Srinivasan and Shetty, 2017; "Eli Lilly drops inhaled insulin program," Reuters, 2008).

In 2014, another insulin product purposed for inhaled therapy, Afrezza® from MannKind, obtained the approval of FDA to improve glycemic control in adults with type-1 and type-2 diabetes. Afrezza® is composed of a thumb-sized delivery device called the MedTone® inhaler (Dreamboat™ inhaler) (Fig. 3B), and a powder formulation contained in a single-use cartridge that must be loaded into the device before each use (Berkenfeld et al., 2015). The drug formulation comprises of Technosphere® insulin inhalation powders, a dry powder mixture of recombinant human insulin-Technosphere® microparticles, with a median diameter of 2.0 to 3.0 μm (Heinemann and Parkin, 2018). The Technosphere® is composed of fumaryl diketopiperazine (FDKP), which is highly soluble at pH > 6 but can self-assemble into microspheres through the process of hydrogen binding in an acid environment (Srinivasan and Shetty, 2017; Easa et al., 2019; Lee et al., 2018; Rahimpour et al., 2014). During the assembly process, insulin in the solution is captured and entrapped when the FDKP precipitates and agglomerates, causing the formation of low-density particles (Berkenfeld et al., 2015). The Technosphere® insulin is preloaded into a color-labeled cartridge with varied strengths: 0.35 mg (4 unit of injected insulin; blue cartridge), 0.70 mg (8 unit of injected insulin; green cartridge) and 1.0 mg (12 unit of injected insulin; yellow cartridge) as shown in Fig. 3 B (Heinemann and Parkin, 2018; Ferrati et al., 2018). This, however, increases the complexity of dosing regime in that the dosage needs to be adjusted based on the individual's metabolism and glycemic control goals.

Although Afrezza® shows superior blood pressure control on diabetes patients, safety concerns do exist. Cough and hypoglycemia are common side effects but are typically mild, while acute bronchospasm and wheezing are also observed after the inhalation of Afrezza®. Therefore, the inhaled Afrezza® must be used under the strict monitoring of healthcare professionals, with a Risk Evaluation and Mitigation Strategy (REMS) to help ensure the benefits of the medication outweigh its risks. During clinical trials, five cases of primary lung cancer were reported and the five patients all had a history of smoke exposure (Balducci et al., 2014). Long-term clinical results also showed two cases of lung cancer in Type-2 diabetes subjects with histories of cigarette exposure and two additional cases of squamous cell lung cancer in non-smokers who received Afrezza® after the clinical trials were completed (Heinemann and Parkin, 2018). More data is required to support its safety profile, especially on non-smoking patients.

2.2. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder caused by dopamine deficiencies, with the most significant motor features being resting tremor, rigidity, bradykinesia, and postural instability (Lipp et al., 2016). Levodopa (LD) is the golden standard when it comes to treating Parkinson's disease due to the upregulation of dopamine level (Clarke and Guttman, 2002). Poor bioavailability of oral levodopa, due to its high peripheral metabolism, is the principal pharmacological challenge the treatment faces. Inhaled therapy has been shown to provide an alternative and auxiliary way to improve its bioavailability as well as being able to instantly deliver in response to the return of Parkinson syndromes (known as OFF period) that renders patients' motor-controlled benefits (Tambasco et al., 2018). Since the OFF period (times of PD patients with difficulties in motor activities which may happen when other medications wear off) will cause patients a great amount of inconvenience and disease burden, a rapid relief of OFF period syndromes is desired (Luinstra et al., 2019). Inbrija®; the first inhaled medication indicated for the intermittent treatment of OFF episodes in PD patients and approved by the US FDA in 2018, was developed to provide a fast and effective alleviation of syndromes for PD patients in need of quick relief (Lipp et al., 2016). It is required to use in combination with carbidopa/levodopa but does not replace the regular oral

Fig. 3. Approved DPI products for systemic disease treatment.

medication(s). The median T_{max} (~30 min; time to peak plasma concentration) after the administration of a single-dose inhaled levodopa powder (84 mg), is shorter than that of an oral carbidopa/levodopa tablet (~45 min, 25 mg/100 mg, immediate-release), resulting in a faster absorption of Inbrija® into bloodstream (Paik, 2020). As for the Inbrija® formulation, the levodopa (42 mg) is specially formulated with 1,2 dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), sodium citrate and sodium chloride, and prepared into large porous particles for effective delivery into the lungs (APV-DD-Newsletter, 2020). The formulation is filled in capsules for oral inhalation and is only used with the breath-activated Cyclops inhaler shown in Fig. 3 C.

Clinical studies have confirmed the practicality, high tolerability and safety of Inbrija® (Patel and Jimenez-Shahed, 2018; Martínez-Raga et al., 2018). Of note, Inbrija® is not recommended for patients with COPD and asthma because of the increased risk of bronchospasm. Today, the levodopa inhalation powder has proven to be an effective and safe strategy for treating symptoms in the OFF period in PD patients, but more clinical data is still required to support its long-term efficacy and safety.

2.3. Schizophrenia

Early identification and prompt intervention that are fast, non-invasive and consensual are common schemes used to de-escalate symptoms of schizophrenia (Gil et al., 2018). Inhaled therapy is one such a preferred way, in which fast onset of the action is achieved and physical restraint to patients is avoided when compared with oral administration and intravenous injection (Pacciardi et al., 2019). Adasuve® is a novel inhalable therapy system, consisting of a hand-held, disposable inhaler and a medication that contains only loxapine (5 mg or 10 mg), in the treatment of acute exacerbation of agitation associated with schizophrenia or bipolar 1 disorder in adults (Gil et al., 2018). Adasuve® employs a single-use delivery system (the Staccato® system) shown in Fig. 3 D to disperse the loxapine powder (Jørgensen et al., 2018). With the Staccato® system, airflow produced by patients is identified by a sensor inside the device, which rapidly heats the loxapine-loaded thin film and vaporizes around 90% of the medication, typically in less than one second (de Berardis et al.; Dinh et al., 2011; Spyker et al., 2014). The medication vapour cools and condenses into aerosols of respiratory size when travelling with airflow, followed by their deposition in the alveoli regions. Overall, Adasuve® allows medication to be delivered directly into the deep lungs, resulting in

rapid absorption and fast relief of symptoms.

One unexpected serious adverse reaction found during clinical trials of Adasuve® is, bronchospasm, which may occur on patients without/with airway diseases. To decrease the possible risk, Adasuve® is prescribed and used in REMS-registered locations, meaning that the drug can be only administered to patients in these health care sites with the capacity to deal with bronchospasm. Although limiting the use of Adasuve® in hospital, a survey on patient's preference on the management of acute agitation is encouraging, showing that the inhaled loxapine is favored over other alternatives due to the fast onsite of action (~2 min), inhalable and limited sedation compared with tablets and injection methods (Jørgensen et al., 2016; Jørgensen et al., 2018). Clinical trial held in Europe investigated the safety and efficacy of Adasuve® when self-administered outside of the hospital setting. The preliminary results showed superior safety profiles on the recruited patients (Gil et al., 2018).

Clinical studies have established the effectiveness, rapid symptom relief capabilities, and safety of inhaled loxapine in REMS-enrolled health care sites; however, its potential for self-administered treatment without the direct supervision of a healthcare professional still needs further confirmation to ensure safe usage (Pacciardi et al., 2019).

2.4. Headache

Migraines are the most prevalent form of neurologic headache in the world (Antonaci et al., Dec. 2016). Particularly, when an acute migraine strikes, rapid pain relief and fast onsite action with minimum side effects are desirable attributes for the treatment to possess (Antonaci et al., Dec. 2016). Inhaled therapy thus proves to be a superior alternative to oral administration when it comes to quickly relieving headaches. Currently, a nasally inhaled dry powder product, Onzetra® Xsail® (AVP-825) used to treat migraines is available in the market. There are also several DPI products for migraine treatment under development. For instance, the MAP0004 Levadex® prepared by MAP Pharmaceuticals, a combination of an inhaler device (Tempo®) with dihydroergotamine as the API, is in development, which can guarantee 2-h pain relief with a short T_{max} of 10 min (Granella, Nov. 2018). In the meantime, another DPI product for migraine treatment, Zolmitriptan (CVT-427), is also being investigated to relieve migraine syndromes with Phase I studies completed (Abdou, 2019). Based on the current situations, inhaled therapy on migraine is presumably feasible and appealing, therefore one can expect their future approval and marketing.

2.5. COVID-19 treatment potential

In the past decades, virus-induced influenza has become a threat to the health or even lives of individuals across the world, especially those in third world countries. In particular, the novel Coronavirus (COVID-19) pandemic began to attack the whole world at the end of 2019, causing an international health crisis. As of September 27, 2021, the virus has caused 231.6 million infections and 4.7 million deaths worldwide (WHO Coronavirus (COVID-19) Dashboard, 2021). This catastrophic situation has triggered intense research and development (R&D) on therapeutics and vaccines against the coronavirus.

Intravenous injection of remdesivir was proven effective in combating COVID-19 in clinical situations (Eastman et al., 2020). In addition to the traditional drug delivery method, inhaled form of therapeutic drugs such as remdesivir also seems to have an edge over other strategies due to its direct delivery to the lesion of the lungs and reduced side effects. Combination therapy of intravenous injection and pulmonary delivery of remdesivir was also recommended in order to obtain a higher level of efficacy against COVID-19 (Sun, 2020). According to research, inhalation through the nebulizer is the fastest and simplest way of implementing direct lung delivery, while dry powder inhalation is suggested to serve as a more convenient alternative if pulmonary drug delivery of remdesivir is deemed safe and effective (Sun, 2020). In late June of 2020, FDA approved a Phase I clinical study of remdesivir inhalation therapy using nebulizers by Gilead Sciences, which aims to provide an easy form of administration outside the hospital during the early stages of COVID-19 disease (Gilead kicks off clinical trial of inhaled remdesivir for less-severe COVID-19, 2021). Moreover, researchers at Texas University developed an inhaled remdesivir powder formulation in an effort to help patients who are not hospitalized, considering that the lung is the primary infection site and boosting of antivirus activity by direct delivery through inhalation to the lungs is logical (Researchers develop dry powder remdesivir to strike COVID-19 where it counts, 2020). These are positive indicators that the potential inhaled therapy possesses for tackling the novel coronavirus disease.

Intaking COVID-19 vaccination using dry powder inhalation would provide a more effective and convenient alternative to the traditional route of vaccine injection, as the powdered vaccine formulation is more stable and does not require stringent storage conditions (Sou et al., 2011; Tonnis et al., 2013; Jahan et al., 2019. To date, 103 vaccine candidates are in clinical development and 184 are in the pre-clinical stage (COVID-19 vaccine tracker and landscape." https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed Jun. 23, 2021)). Encouragingly, COVID-19 vaccines authorized for emergency use, such as Pfizer-Biotech vaccine in US and Oxford-AstraZeneca vaccine in UK, have been approved. The majority of the vaccines administered by intramuscular injection is in liquid form and stored under freezing conditions to keep their immunoactivity. This causes challenges during vaccine distribution, particularly in remote and tropical areas. As such, the inhaled delivery of dry powder vaccines has been proposed as a superior alternative in order to protect people from catching COVID-19 while alleviating transportation difficulties and reducing cost. Due to its stable formulation and not requiring cold chain transportation, dry powder vaccines offer more options for treatments, as well as providing prophylaxis for patients in developing countries. In addition, given that the mucosal membrane is the primary invasion and infection site for the virus, the direct and local immunization and protection facilitated by the inhaled dry powder is more beneficial (Sou et al., 2011). At the same time, dry powder vaccines also decrease the risk of transmitting other possible bacteria or virus by not requiring a needle, and boost the patient compliance, and it is not essential to have trained healthcare professionals for the vaccination process (Foged, 2016). Currently, several companies have reported improved versions of COVID-19 vaccines inhaled through nebuliser. For instance, a clinical research reported an in-development COVID-19 vaccine utilizing nebulisers, where the vaccine is aerosolized into airborne droplets and delivered to the airways (Trial will assess safety of potential vaccines when inhaled, 2021). CanSino Biologics Inc. also received approval for a clinical trial for their improved inhaled COVID-19 vaccine. Additionally, ISR (Immune System Regulation), an immunotherapy research company, is developing an inhaled dry powder COVID-19 vaccine in cooperation with Iconovo, a leading Swedish company offering inhalation platform (ISR and Iconovo agree to develop inhaled Covid-19 vaccine, 2021).

In addition to the DPI products used for treating systemic diseases discussed earlier in this section, there are many more examples of therapeutic drugs in development. For example, a potent drug candidate developed for cancer pain relief, fentanyl, using a TAIFUN inhaler as the dry powder delivery device, has been shown to achieve a rapid onset of action in less than 2 min and demonstrates a higher level of bioavailability in an *in-vivo* study (Overhoff et al., 2008). Heparin, an anticoagulant that prepared into large inhalable porous particles, showed the ability to be effectively delivered to the lung through inhalation, all while exhibiting satisfactory release property and the viability of Calu-3 cells (Rawat et al.,2008). Using inhalable dry powder vaccines to treat diseases like measles, influenza virus and malaria, were also investigated with significant success (Islam and Cleary, 2012).

3. Advancements on DPI formulations

The drug formulation plays an important role in the effective delivery of drug powders to the lungs. There are numerous formulation-related physiochemical factors with remarkable influence on lung deposition, including surface roughness, morphology, crystallinity, surface energetics, drug to carrier ratio, particle diameter and density, electrical charge, or hygroscopicity (Groneberg et al., 2003; Murnane et al., 2009). Since the advent of dry powder inhaler products in the mid-1960s, the traditional drug-only formulation or drug-carrier mixture formulation have been extensively studied. In the past ten years, novel inhalable particle systems with varied drug delivery purposes are also gaining increasing attention. For example, the lungs have two clearance pathways, the ciliary system for the clearance of airborne particles deposited in larger airways and the alveolar macrophage for clearance of particles deposited in air sacs. If the systemic therapeutic effect is desired, avoiding the macrophage clearance will be an issue of concern. If the sustained-release profile is desired, extending the retention time of drug formulation in the periphery lungs will be another issue that requires additional attention. Therefore, novel and smart drug formulations need to be engineered in order to solve the possible problems. This section provides an overall review on the advancements of novel dry powder formulations, most discussing microparticle system and nanomedicine system.

3.1. Microparticle system

The microparticle system of inhalation usually employs polymer-based particles in order to achieve sustained-release, longer retention, mucoadhesiveness, and the escape of macrophage uptake (Kutscher et al., 2010; Ni et al., 2017). Usually, polymers used in microparticle system include chitosan (CS), gelatin, hyaluronic acid (HA), poly(lactic acid) (PLA), poly(vinyl alcohol) (PVA) and poly(lactic-co-glycolic acid) (PLGA), among which PLGA is the most comprehensively exploited due to its excellent biocompatibility and capability of tuning the drug release rate (Liang et al., 2015). Vaccines, antibodies, DNA, RNA as well as small molecules can also be incorporated into these carrier systems by tailoring formulation to achieve different therapeutic goals.

Major improvements in aerosol performance can be achieved by lowering the particle density and increasing the particle geometric size (Ungaro et al., 2006). Large porous particles (LPPs), by virtue of their porosity, exhibit an aerodynamic diameter much smaller than their geometric size, facilitating excellent flowability and improved dispersion (Chvatal et al., 2019). For example, the emulsion evaporation method enables the production of light porous particles that display an improved flowability and deep lung deposition (Gharse and Fiegel, 2016). Therefore, LPPs are highly efficient in the delivery of inhaled therapeutics into the systemic circulation. Furthermore, the large geometric size of LPPs can reduce their clearance by macrophage action, thereby improving the bioavailability of the inhaled pharmaceuticals (Yang et al., 2019).

Swellable microparticles is another novel system that has been well studied in the pulmonary drug delivery field. Swellable and mucoadhesive materials such as CS, HA and hydroxypropyl cellulose (HPC) are engineered with API into inhalable microparticles within the respiratory size range. Such microparticles posses the capability to swell into larger sizes after depositing and interacting with lung line fluid, which helps avoid phagocytosis by macrophages and achieve longer lung retention. The research group led by Mao found that a swellable CS can achieve a sustained release of drug in the lungs and provide a longer retention time, both of which can be adjusted by incorporating other swellable materials with different structures and charges (Wang et al., 2018; Zhang et al., 2018).

3.2. Nanomedicine system

Over the past years, nanotechnology has been introduced into our daily life and also into the pharmaceutical field. Nanomedicine, typically with medications within the nanometer scale, has demonstrated great potential as inhalable therapeutics. The most outstanding feature of nanomedicine is its capability for targeted drug delivery, via either passive or active routing. Passive targeting is achieved by the preferential transportation of nanomedicines into tumour areas through enhanced permeation and the retention effect (EPR effect) (Zhu et al., 2019). Active targeting, which tends to be more efficient, is achieved by the tailored design of nanomedicines through conjugating ligand on its surface to receptors on specific cell membranes of the tumour (Rosière et al., Mar. 2019). Therapeutics including small molecules, peptides, proteins, and nuclei acids, have been studied to be engineered into inhalable nanomedicines for disease treatment (Alabsi et al., 2021; Teymouri Rad et al., 2019; Tran et al., 2020). Apart from treating respiratory and systemic diseases, inhaled nanomedicines also presents potential applications in biomedical diagnostics and imaging (Das et al., 2021). These studies show great promises of inhaled nanomedicines for the forthcoming clinical use.

Using liposomes for pulmonary delivery is an excellent way to encapsulate and deliver either hydrophilic or hydrophobic drugs (Ohnishi et al., 2015). Liposomes have highly organized self-enclosed and small spherical structures, consisting of one layer (unilamellar liposomes) or multi-layer lipid membranes (multilamellar liposomes), with a size range of 50 to 1000 nm (Gaspar et al., 2008). The liposomes are prepared with a wide range of phospholipid materials such as phosphatidylcholine (PC), dipalmitoyl phosphatidylglycerol (DPPG), DPPC, DSPC and cholesterol (Mehta, 2016). The large lipid content of liposome guarantees high biocompatibility with the pulmonary surfactant system, and reduces the possible accumulation of other excipients (Gibbons et al., 2010). Additionally, the physiochemical properties (size, loading capacity, surface charge, permeability) of drug-loaded liposomes can be modified to achieve specific drug delivery goals. Currently, extensive studies on inhalable liposome formulations have been carried out and some of the products have been tested in clinical trials. The first and the only liposome product used for oral inhalation, Arikayce® (amikacin liposome suspension), was approved by FDA in 2018 for the treatment of *Mycobacterium avium* complex lung disease, thus proving the feasibility of the inhaled liposome formulation. The dry powder form of the liposome formulation that reconstitutes after the powders reach the lungs, is still under development but has demonstrated some potential. The inhaled clarithromycin liposomal dry powders prepared by Wang and Chan's team showed improvements in aerosol performance, providing an emitted dose of over 85% and mass fraction of fine particles within 5 μm up to 50% (Ye et al., 2017). An inhalable docetaxel liposome dry powder formulation using PC as the lipid material designed for lung cancer therapy, was successfully prepared by Zhu *et al.*; and exhibited outstanding tumor targeting properties and produced less side effects in comparison with the intravenous administration route (Zhu et al., 2019). These advancements demonstrate the potentiality of liposome-based dry powder formulation and portrays the likelihood of inhaled therapy being used in the future.

Biodegradable polymeric nanoparticles (NPs) function as another promising vehicle for the delivery of small molecules as well as macromolecules like peptides, proteins, antigen and DNA due to the increasing attention for pulmonary drug delivery (Kunda et al., 2015). Polymeric NPs are submicron systems where drug particles are dissolved, encapsulated, adsorbed or linked with polymers (Pridgen et al., 2014). Polymers used for the NP system are categorized into two types: 1) natural polymers such as CS, alginate; and 2) synthetic polymers like PLGA, PLA. Polymer-based NPs have a number of strengths: modified surface properties, high drug loading, protection against degradation, sustained release, a long shelf life, and the ability to bypass physiological membrane like the blood-brain barrier (Ding and Zhu, Nov. 2018;

Paranjpe and Müller-Goymann, 2014).

Aside from liposomes and polymeric NPs which have been discussed above, other nano-scaled inhalable drug delivery systems also have been studied, such as the nanostructured lipid carrier system, hybrid lipid-carrier system, lipid nanocapsule system, inorganic nanocarrier system, nanoemulsion system, and nanocomplex system (Abdelaziz et al., 2018; Pepic et al., 2014). The development of inhalable nanomedicines is advancing quickly, and further studies on nanomedicines with new or improved properties are expected.

4. Advancements on DPI devices

The breath-activated passive inhalers are mainstream but also has their limitations. They are often too dependant on the patient's inspiratory flow. Typically, low intrinsic air resistance inhalers allow easy airflow through the device but may not have enough dispersion and de-aggregation for effective drug delivery, whilst the high-resistance inhalers would generate a stronger turbulent flow and improve disaggregation but require a higher inspiratory effort, which cannot be achieved by patients who suffer from an airflow limitation. Therefore, novel device designs are made to improve the performance of inhalers, including energy-powered active inhalers and digital inhalers.

4.1. Active devices

In the past two decades, energy-powered active DPIs have been proposed and are advancing quickly. They are less dependent on the inspiratory airflow of patients but more on external sources of energy, such as battery motors (Spiros®), piezoelectricity (MicroDose®) and compressed air (Exubera®, Aspirair®), to fluidize and disperse the dry powders. These active devices are particularly more suitable for children and elderly patients (Srinivasan and Shetty, 2017).

The Spiros® DPI (Fig. 4) is a battery-powered system. It is a small (6 cm × 10 cm), handheld, breath-actuated device. The circular disk-shaped cassette has 30 wells, each containing a pre-loaded drug/lactose mixture. One dose is loaded into the aerosolization chamber with one opening and closing practice of the inhaler lid. Inhalation is sensed by a switch that will activate a small built-in motor (LiCalsi et al., 1999). Subsequently, the battery energy is converted into mechanical energy through the motor, which drives the high-speed rotation of a twin-bladed impeller in the aerosolization chamber to disperse the powder blends (Nelson et al., 1999). Therefore, the Spiros® device is less dependent on patients' airflow and requires an inhalation flow rate as low as 5 L/min to work, making it advantageous for pediatric and elderly patients with limited airflow (Srinivasan and Shetty, 2017).

MicroDose® DPI (Fig. 5) is a piezoelectricity-powered system that can convert electric energy into mechanical motion to disaggregate the formulation powders. It has a circular blister cartridge with drug blends contained in each blister. A blister is punctured before inhalation. Upon activation by inhalation, a built-in piezoelectric vibrator will generate a high-frequency vibration to aerosolize drug powders (Title: Supercharging The Dry Powder Inhaler | Medgadget, 2021). At the same time, the fine de-aggregated particles migrate from the bulk to the pieced holes while being aerosolized and inhaled by patients. The device is sophisticated, but is claimed to have a cheap unit manufacturing price (Newman, Jan. 2004).

The Exubera® DPI (Fig. 6) is a compressed air–powered system consisting of three main parts: an inhaler base, release unit and chamber. The base contains an air pump, a canister and a valve, which are responsible for compressed air generation, storage and release. At the base, ambient gas is drawn in to have a fixed gas volume of 8 mL compressed and stored in the canister after one operation of the pump handle (Harper et al., 2007), which simultaneously pierces the inserted blister. Upon the actuation of the device, the compressed air is released through a jet structure in the release unit. The jet structure then creates a vacuum, drawing the powder in the blister into the release unit. At the time, a sonic discharge of powder into a 300 mL chamber will occur, which accelerates and violently mixes the power and generates a standing aerosol cloud, ready to be inhaled by the patients. This practice requires not only less coordination between the actuation and inhalation, but also less inspiratory effort to operate the device when compared with other DPIs, albeit the large size and the multi-operation procedure required for using the Exubera® DPI. Another active DPI, Aspirair®, also utilises pressurised air as external energy for powder disaggregation.

The design of active devices allows the external energy source to fluidize and aerosolize the powder bed in the DPI instead of inspiratory airflow of patients. This makes it easier for patients with limited airflow to inhale the therapeutic powders as a fast inhalation is not necessarily required for efficient pulmonary drug delivery.

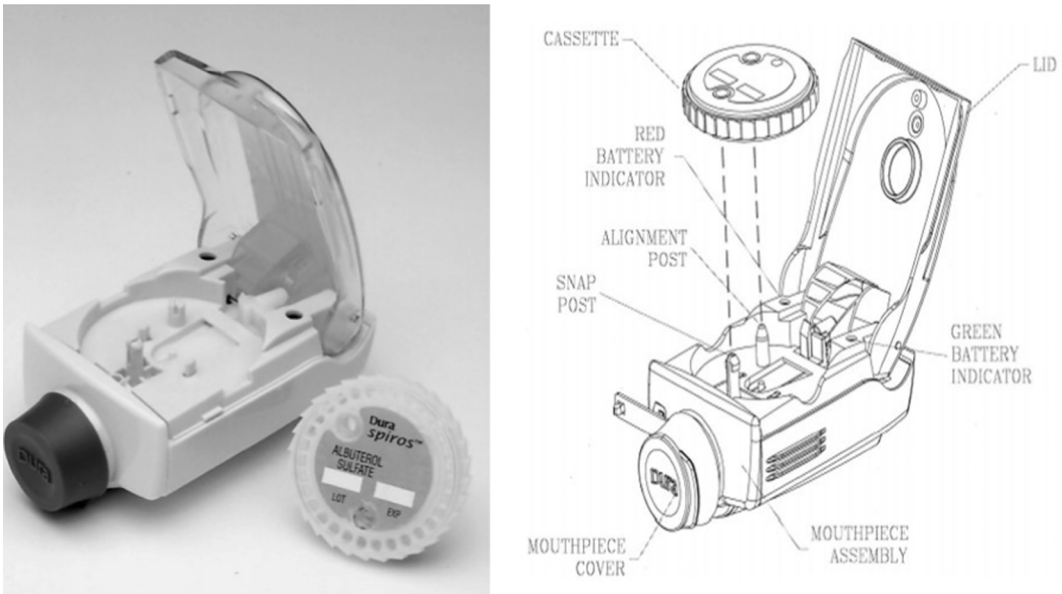

Fig. 4. Spiros® DPI with a cassette.
Adapted from Geoffroy et al., 1999; Nelson et al., 1999

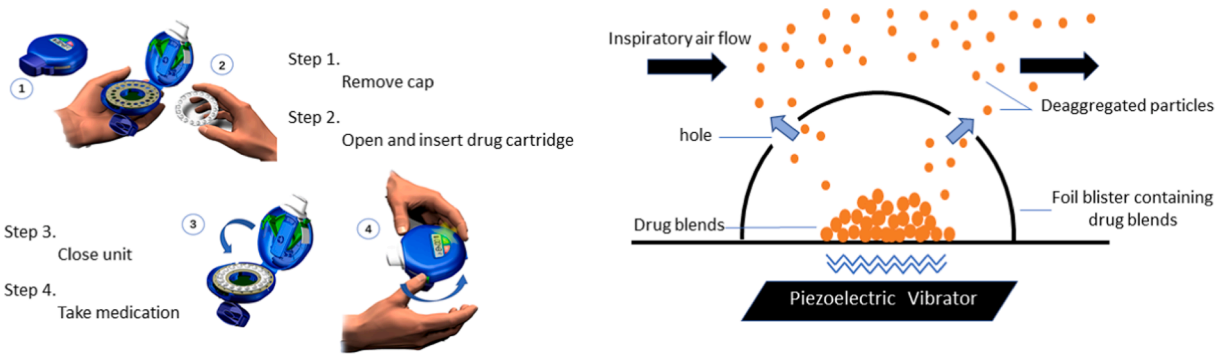

Fig. 5. MicroDose® DPI and mechanism to actively aerosolize aggregated particles.
Adapted from "Title: Supercharging The Dry Powder Inhaler | Medgadget." https://www.google.com/imgres (accessed Jun. 17, 2021; Al-Tabakha, Oct. 2015)

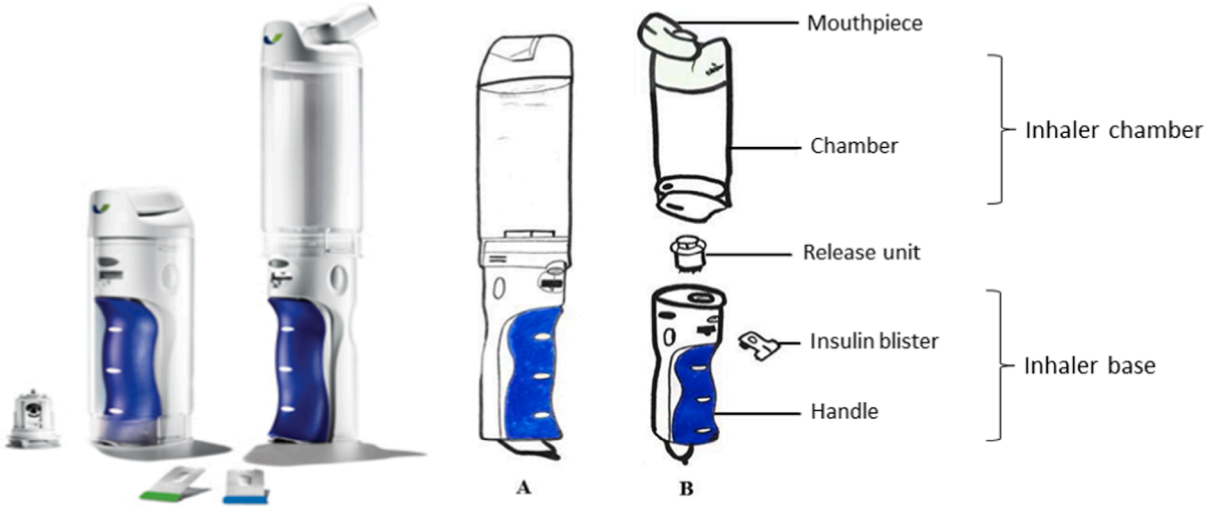

Fig. 6. Exubera® DPI.
Adapted from Al-Tabakha; Pfizer and Nektar resolve Exubera contract, 2007

4.2. *Digital devices*

Patient's adherence to the prescribed medications and the correct use of techniques plays a significant role in the successful and effective inhalation therapy . Most patients however, may forget to take their medicine on time and 70% to 80% of them do not use their inhalers correctly, therefore greatly increasing the healthcare costs (Taylor et al., Mar. 2018). To tackle these two main issues, digital inhalers are developed and have been gradually emerging in the market in recent years. Digital inhalers are smart devices incorporating digital technologies with additional drug-administration purposes, such as detecting and recording inhalation information, data transmission to a mobile application or website for further guidance, alert on ambient environment and incorrect use, and setting reminders for patients to take their medicine. The digital inhalers are primarily designed to improve medication adherence for patients (Blakey et al., 2018; Taylor et al., Mar. 2018; Mehta, Jan. 2021). The product, ProAir® Digihaler® (Fig. 7A) from Teva, has secured FDA-approval as the first and only

Fig. 7. Examples of digital inhalers wirelessly connecting to a mobile app: A) ProAir® Digihaler® ; B) The Respiro® system attached to an Ellipta DPI; C) Enerzair® Breezhaler®.
Adapted from Amiko Respiro Inhaler Tracking System Cleared in Europe | Medgadget, 2021; Novartis receives EC approval for Enerzair® Breezhaler®, including the first digital companion (sensor and app) that can be prescribed alongside a treatment for uncontrolled asthma in the EU, 2021; Philippidis, 2018

digital inhaler with a built-in sensor and mobile app (Philippidis, 2018). Digihaler® employs a sensor for measuring inspiratory flow, recording time of use, and transmitting data to a mobile application. The data can then be shared with healthcare givers, allowing them to provide better personalized medication for the patients. Another digital product is the Respiro® system developed by Amiko Digital Health, which also uses an add-on or built-in sensor to capture flow data through the inhaler, and can provide real-life use and help healthcare professionals better understand the effectiveness of inhalation therapy (Amiko Respiro Inhaler Tracking System Cleared in Europe | Medgadget, 2021; Sloots et al., Jul. 2021). A mobile app is also incorporated into the system as a companion to the sensor, helping remind patients to inhale a dose and even provide AI-powered therapy suggestions. An example of its application is the Ellipta inhaler with an add-on Respiro® system as shown in Fig. 7B. Enerzair® Breezhaler®, a digital inhaler product from Novartis, obtained the approval of European Commission to treat uncontrolled asthma . The approval also includes an optional digital companion with a sensor and app shown in Fig. 7C, providing inhalation confirmation and reminder and other objective information to better support therapy decisions (Mehta, Jan. 2021).

Digital inhalers not only offer therapeutic benefits to the patients, but are also able to better monitor on patients' adherence to prescriptions, inhalation conditions and development of diseases, to the healthcare professionals. Undoubtedly, they point to the future direction of dry powder inhaler devices.

4.3. Devices for respiratory vaccine delivery

As discussed earlier in Section 2.5, inhalable powder vaccines possess more benefits than those in liquid form, whether being through injection or nebulization. A DPI device is an indispensable component for powered vaccine delivery by inhalation, but what kind of DPI device is more suitable? Other than the common requirements for DPIs, such as fine aerosolization performance, device reliability, ease of use and patient compliance, a preferable DPIs for vaccination should also have the following key attributes:

(1) simple to administrate and easy to learn, thereby minimising the need of trained healthcare personnel for vaccination;
(2) simpler structure and fewer parts and therefore lower cost, thus favouring affordable production for mass immunization;
(3) better lung deposition and efficacy, without needing forceful inhalation, suitable for vaccination of patients with limited airflow;
(4) single-use prevision only, not requiring frequent and continuous dosing under most conditions (de Berardis et al., 2017; Friebel and Steckel, Dec. 2010; Heida et al., 2021). Until now, single-use DPI systems for vaccination use have not been widely utilized with regulatory approval but some products for non-COVID uses have reached the clinical phase (Friebel and Steckel, Dec. 2010). Two potential disposable DPIs for vaccines are presented in Fig. 8.

The Puffhaler shown in Fig. 8A uses a bulb and a burst valve system to aerosolize the powder in an aluminum foil blister. The generated aerosol fills in a plastic bag reservoir, allowing for simple inhalation ("Puff Inhale") (Jahan et al., 2019). The Solovent system (Becton, Dickinson and Co.) was principally developed to deliver powder-form vaccines into the lungs or nasal cavity through a single inhalation ("Solo Vent") (Friebel and Steckel, Dec. 2010). It uses a syringe to pressurize the powered vaccine contained in the capsule as shown in Fig. 8B. A thin film sealing the capsule is ruptured when the pressure rises to a threshold, and the powder inside the capsule is expelled into the spacer for pulmonary delivery through a patient interface (Tonnis et al., 2013). Both Puffhaler and Solovent are active devices, and have shown successful *in-vivo* respiratory vaccine delivery and immunization for treating measles (Lin et al., 2011). In addition, there are other disposable DPIs that also possess great potential for delivering inhalable vaccines, such as the SOLO inhaler (Disposable DPI, 2021), a passive DPI from Manta, TwinCaps (TwinCaps, market approved disposable inhaler, 2021), a preloaded passive DPI from Hovione, and Occoris (Banks, 2013), an active device from Team Consulting, as shown in Fig. 9.

In summary, the ideal design of DPIs used for respiratory vaccination should be simple, cheap, disposable and effective and most likely single-dose. The above discussion provides some basic guidelines for designing the most effective DPIs for COVID-19 vaccination as well as vaccinations for other diseases.

5. Unmet problems and possible solutions

5.1. Excipient safety

Pulmonary drug delivery is completely different from traditional drug delivery systems: (1) Excipients used in oral solid dosage products, are mostly not suitable for lung delivery systems; (2) The lung surfactants may not be as abundant and numerous as that in the intestinal system; (3) The extent and rate of drugs and excipients that can be metabolized are different from that in the intestines. Therefore, the safety and reliability of excipients should be guaranteed before being used as components of the pulmonary delivery system. Particularly, when a large amount of exogenous materials are present in lungs for a long duration, it will likely result in the accumulation of themselves and/or their degradation products, leading to other potential consequences (Liang et al., 2015). The potential safety risks caused by

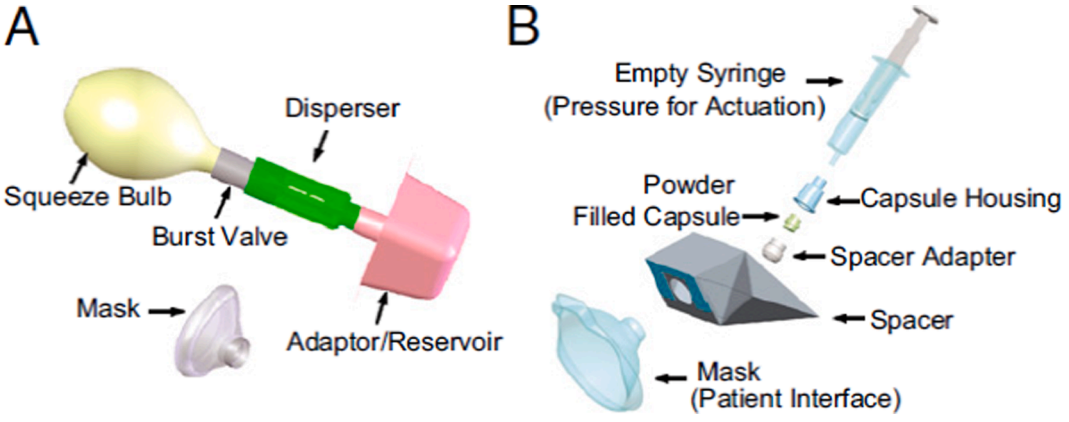

Fig. 8. Examples of single-use DPI for vaccination purpose. A) Puffhaler; B) Solovent.
Adapted from Lin et al., 2011

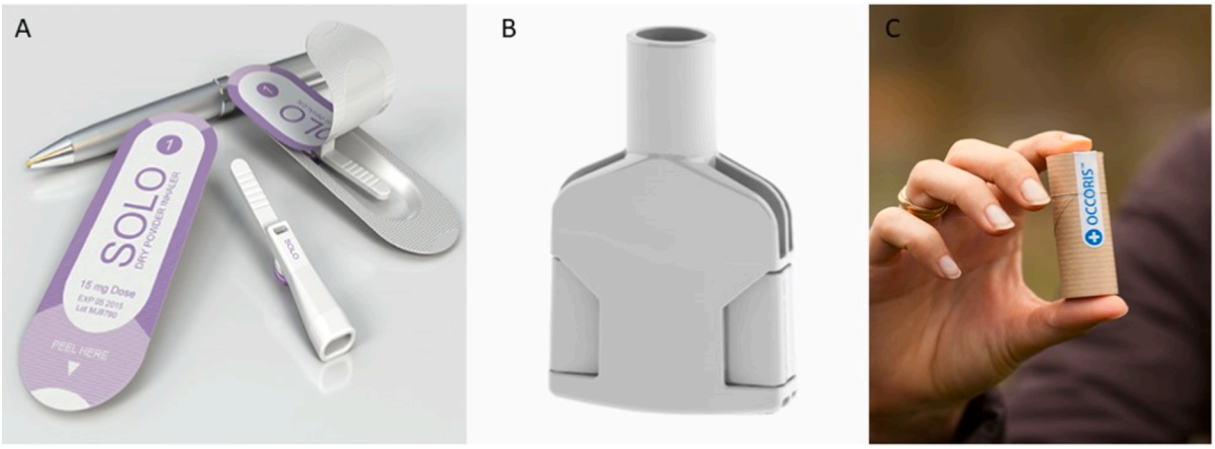

Fig. 9. Examples of disposable DPI for vaccination purpose. A) SOLO; B) TwinCaps; C) Occoris.
Adapted from Banks, 2013; Disposable DPI, 2021; TwinCaps, market approved disposable inhaler, 2021

excipients, may hinder their use for pulmonary drug delivery. For instance, PLGA-50:50 (ratio of Lactide to Glycolide) has been extensively exploited in sustained-release formulations for pulmonary drug delivery in a research scale, yet its half life is long, approximately 60 days. PLGA and its metabolites, lactic acid and glycolic acid, may be present in the lungs for extended time, leading to accumulation, a low acidic environment and further negative influence on lung functions. It was reported that lactic acid, in the case of PLGA, can increase inflammation of the airways and decrease cell viability (Cook et al., May 2005).

Toxicity has also been shown in a comparative study for several other polymeric excipients, including HPC, alginate, CS, gelatin and ovalbumin (Sivadas et al., 2008). Alternative materials with confirmed safety profiles are therefore needed and phospholipids has been reported as a being a better choice. Lipids such as DPPC, DSPG (1,2-Distearoyl-*sn*-glycero-3-phosphoglycerol), are endogenous to lungs and are generally recognized as safe excipients that can be rapidly metabolized and eliminated from the lungs after deposition in the lungs (Daniher et al., 2020; Pilcer and Amighi, Jun. 2010). DPPC is a naturally occurring phospholipid and is a major component in lung surfactant system (40% by weight) (Eedara et al., Jun. 2016). DPPC has been proven to function as a lipid material that can be used as an excipient in drug-loaded liposomes for the treatment of pulmonary bacterial infections (Castoldi et al., 2017). DPPC was also used as a water-insoluble material for spray-drying in order to prepare porous particles and as a penetration enhancer that improves the permeability of medications in deep lung (Morales et al., May 2011). No DPPC-related safety issues have been reported until now, which means that DPPC has potentially a better safety profile than other polymers, although long-term safety data is still required. One product with DPPC as the excipient is the AIR® insulin inhalation powder, which had shown no indication of any negative effects of DPPC at the cellular level (Angelo et al., May 2009).

Lactose is the only excipient approved by the FDA and EMA for wide use in pulmonary drug delivery and has been extensively formulated around the world. There are however also some issues with lactose, such as the Maillard reaction with amine-contained APIs, low intolerance in some patient populations and sometimes displaying disappointing aerosol performances (Rahimpour et al., 2014). The limited diversity of excipients in dry powder formulation expedites researchers to develop alternatives that could be safely and widely used in this field.

5.2. Lung deposition

There has been a rapid growth in the popularity of dry powder inhaler products used for treating local and systemic diseases in the past decades, yet challenges on the formulation still exist. Fine particle fraction (FPF), the mass percentage of drug particles with an aerodynamic size within 5 μm, is an essential parameter for assessing *in-vitro* aerodynamic performance of aerosols (Mendyk et al., 2015). At present, a major issue with aerosol delivery is the low fine particle fraction with a great variation (Islam and Cleary, 2012). The lung deposition of most marketed DPI products varies from 10% to 40% with a significant fraction being left at the patients′ mouth-throat (Geller et al., 2011; Weers et al., 2015). The oropharynx deposition of several approved DPIs, as summarized by Hak-kim Chan *et. al.* (Yang et al., 2014) can reach up to 80%. This was ascertained as a primary determent of lung deposition and is considered highly related to variability in lung deposition (Borgström et al., Dec. 2006).

Theoretically, high *in-vitro* drug delivery is regarded as a positive indicator of good *in-vivo* lung deposition and therapeutic effects. However, this may not be necessarily true, as a poor correlation of *in-vitro* and *in-vivo* deposition may come from the failed use of realistic throat models and the different breath patterns of each individual (Weers et al., 2015). Moreover, the orally inhaled powder will undergo dissolution, clearance and permeation process after coming in contacting with lung line fluids, which may lead to more significant differences. The primary related factors that affect the bio-performance and final effectiveness of inhaled medicines are listed in Fig. 10. It is not easy to characterize their bio-performance but it is essential and critical to establish a more reliable *in vitro–in vivo* correlation (IVIVC) when developing formulation-device combination systems, which will help predict the *in-vivo* performance through *in-vitro* testing.

5.3. Aerosolization performance and acceptability of inhaler device

In the past several decades, oral inhalation has been developed as a promising and effective method for pulmonary disease treatments. Although possessing unique advantages, faster onsite action and less side effects when compared with traditional tablets and pills, these developed inhaled products have not been widely used other than for asthma and COPD. The dry powder version has been used by an even smaller number of patients due to limited acceptance and patient preferences. The failure of Exubera® also confirmed the importance of patient's acceptance, as discussed earlier in the review.

In the meantime, DPIs, which have appeared on the market, are gradually evolving to be easier to use and provide better aerosolization. Most approved DPIs are breath-activated, relying solely on the patient's inspiratory effort to fluidize and disperse the powdered formulation. Patients with severe airway diseases however, have difficulties generating sufficient airflow, which may reduce the emission of an aerosol from the device and the penetration of drug particles into lungs). Therefore, another limitation with current DPIs is that the delivery of

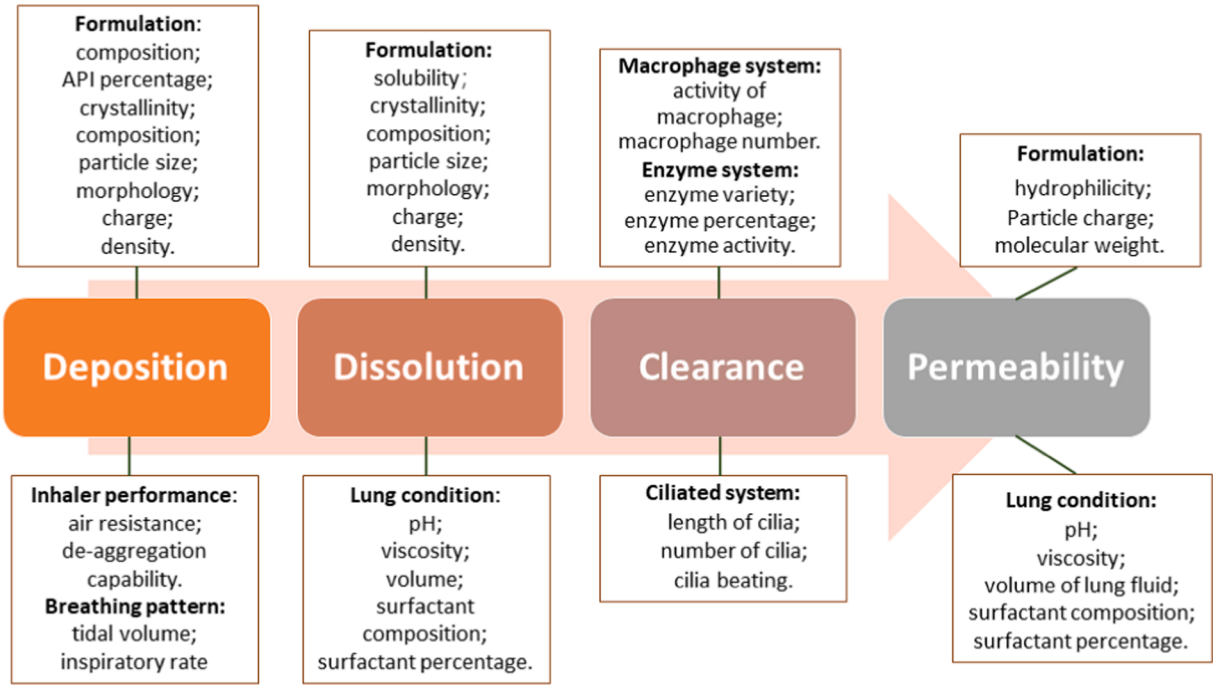

Fig. 10. Factors affecting the bio-performance of inhaled medicines.

drugs is often too dependent upon inspiratory flow rates for good efficacy. Turbulent flow and particle-inhaler or particle-particle collision are usually introduced to increase the disaggregation of drug particles and/or de-attachment of drug particles from carriers, but this may result in higher air flow resistance, making easy inhalation more challenging to achieve. It is thus difficult to reach a balance between good dispersion capabilities and attaining easy inhalation when designing DPIs.

Encouragingly, the advent of energy-powered and digitally monitored DPIs provide new insights on effective drug delivery to the lungs and are able to overcome the strong dependence on the inspiratory flow of patients, as discussed prior in this review. However, whether those advancements would overweigh their high pricing is yet to be seen when it comes to patient's selection of DPI products. To date, a perfect DPI product with cost-effectiveness, reliability, robustness and perfect aerosolization performance, has not been seen. There is still a long way to go for the development of an ideal inhaler device, and success may be on the horizon.

6. Conclusions

This article attempts to provide a thorough review on the detailed formulation and device information as well as clinical status of the approved and in-development DPI products used for the treatment of systemic disorders. Since the mid 1960s, pulmonary drug delivery by dry powder inhaler for lung diseases, particularly asthma and COPD, has shown great successes in wide clinical practices. Such success has also triggered the advent of inhaled therapy for systemic diseases since the lung was often viewed as a powerful portal of entry to systemic circulation for a broad range of therapies. While it seemed as if many inhaled dry powder medications that treated systemic disorders would have boomed to the market, the reality is not as cheerful as one would have expected. Only a limited number of inhalable products have been approved and marketed due to undesirable incidents involving side effects and unclear long-term safety, as well as the poor acceptance of patients on inhaler systems. The withdrawal of Exubera® and the discontinuation of Lily's inhalable insulin project had left much uncertainty, not only on the future of inhaled therapy for systemic disorders but also on the future of inhaled therapeutic proteins and peptides in general.

While having not been as optimistic as one expects, research development on powder formulations and DPI devices designed for systemic diseases continues on with comprehensive studies on novel and smart pulmonary drug delivery formulations, including the microparticle and nanoparticle systems. Sophisticated formulations have been tailor-made to achieve different formulating purposes: (1) for sustained release and extended release by using compatible and safe polymers; (2) for extended retention in the lungs by avoiding the clearance of the defense system, using swelling mechanisms or larger porous particles; and (3) for active targeting by applying EPR effects and for passive targeting by conjugating ligands with receptors.

The design of dry powder inhalers is also gradually evolving with much progress. To decrease inhaler misuse, DPIs are made to be simpler and easier to use. To avoid dependence on patients' airflow when using passive inhalers, active DPIs appear to become more popular with new designs proposed to help aerosolize and disperse drug powders, albeit probably implying in cost ineffectiveness and unsatisfactory sale volume. To improve patient compliance with DPIs, digital inhalers are emerging on the market equipped with fancy and practical functions such as setting reminders, alerts, monitoring, data collection and information transmission. Those smart DPIs bring more therapeutical benefits to both patients and healthcare givers, and more can be expected to reach the market in the near future.

In spite of the advancements, there still exist formulation and device-related challenges, with major unsolved problems regarding the limited selections of viable excipients, low and variable lung deposition, less desirable cost-effectiveness, and poor inhaler performance and IVIVC. Despite ups and downs in the past and challenges ahead, one should still hold hope for pulmonary drug delivery on the treatment of not only respiratory symptoms but also systemic diseases.

Based on the success of inhaled products, DPI applications has also been extended to vaccines and antivirus drugs. Amid the difficult times created by the COVID-19 pandemic, pulmonary vaccinations have shown great potential and is a more viable alternative for combating the pandemic.

Credit author statement

Yuqing Ye: original drafting, investigation, visualization, editing. **Ying Ma:** project administration and review. **Dr. Jesse Zhu:** funding acquisition, project administration, review and editing. All authors have given approval to the submitted manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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