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Review on Dry Powder Inhalation Drug Delivery for Lung Disease

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ABSTRACT

Dry powder inhalers (DPIs) are an important and growingly researched current therapeutic approach for a growing range of respiratory disorders. DPIs are a viable choice for some patient populations, and they may assist overcome various difficulties associated with other types of aerosol delivery systems (e.g., dose accuracy and repeatability, compliance and adherence issues, or environmental considerations). There are currently over 20 different dry powder inhalers on the market that deliver active pharmaceutical ingredients (APIs) for local and/or systemic therapy. Dry powder inhalers operate differently depending on the method of deagglomeration, aerosolization, dose metering precision, and interpatient variability. Manufacturers work on improving aspects of their individual DPI devices during development, based on the intended type of application and any special needs linked with it. There are a variety of different devices with distinct features because to the large range of applications associated to specific APIs. In addition to the commonly used multi-use DPIs, some single-use disposable devices are in the works or have previously been certified. With the recent introduction of disposable devices, the range of prospective applications for utilisation will be expanded to include compounds such as vaccinations, analgesics, and even rescue drugs. This review article addresses the performance and benefits of recently approved dry powder inhalers as well as disposable single-use inhalers in development.

Introduction

With the development of commercially available pressurized metered dosage inhalers (pMDIs) for the treatment of asthma by Riker Laboratories in 1956 [1], drug delivery to the lungs became widely accessible in modern clinical practice for the first time. Although this was a watershed moment in the treatment of respiratory disorders, concerns arose in 1974 when the involvement of chlorofluorocarbon (CFC) propellants to ozone layer depletion was hypothesized [2]. CFCs were subsequently replaced in 1995 with more environmentally friendly hydrofluoroalkane (HFA) gases, which were proved not to affect the oxygen/ozone equilibrium in the upper stratosphere [3-6], as stipulated by the Montreal Protocol in 1987.

It has since been discovered that HFA gases are up to 2000-fold more potent as greenhouse gases than carbon dioxide, but contributing less than 0.1% to global greenhouse gas emissions [7,8]. pMDIs may potentially encounter issues due to the propellant employed [9,10]. Depending on whether the medicine is manufactured as a solution or a suspension, concerns such as low solubility [11] and chemical instability of the active pharmaceutical ingredient (API) [12] or crystal formation phenomena [13] and suspension instability [14] develop. This may result in incorrect dosing and a reduced drug loading capability.

Furthermore, as potential downsides for pMDI formulations, the low efficiency of medication targeting to the tiny airways and reformulation issues have been noted. Clinically, broncho-constriction difficulties (i.e., Freon effect) [15] and/or the necessity to activate the pMDI delivery device simultaneously with patient inspiration and a complex inhalation manoeuvre may limit patient compliance, particularly in specific patient subpopulations [16,17]. The introduction of dry powder inhalers (DPIs) was one method to overcoming these restrictions. Fisons (Ipswich, UK) introduced the Spinhaler® device in 1967 [7]. Since then, great developments in DPI technology have been made, with various devices entering the market, while pMDIs continue to be the most popular and widely utilised technology due to their widespread acceptability and simplicity [18].

There are now around 20 different DPI devices available from various manufacturers, with several more in development or clinical studies. Aside from the traditional treatment of airway illnesses such as asthma and chronic obstructive pulmonary disease (COPD) [19], various inhalable solutions for systemic drug administration have already been licenced and are on the market [20], or are in

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the works [21,22]. Furthermore, there is a growing interest in the development of single-use disposable dry powder inhalers [23]. This review will provide an update on recently approved and novel DPI devices, as well as an overview of the most recent advancements in the development and approval of single-use dry powder inhalation devices.

Requirements for Dry Powder Inhalation Devices

Inhalation devices are intended to deliver a predetermined dose of a medicine to the tiny airways and alveolar portion of the lung in a repeatable manner. Particles having a mass median aerodynamic diameter (MMAD) of 1-5 μm have been observed to be successfully deposited at the aforementioned places [24]. The MMAD of a particle is determined by its geometrical diameter, density, and shape, all of which are generally adjusted throughout the manufacturing process [25]. Micronized powders are particularly adhesive/cohesive, spontaneously forming agglomerates due to inter-particulate forces such as mechanical interlocking, capillary, electrostatic, and vander Waals forces [26].

The amount of the partial and, as a result, combined forces is determined by powder parameters such as particle size, morphology, shape, and material [27], as well as environmental conditions such as relative humidity [28]. Because the degree of agglomeration influences the proportion of inhaled powder that is within the respirable range [29], these agglomerates must be properly deagglomerated prior to or during the aerosolization and inhalation procedures [30]. DPIs that use a patient's inspiratory airflow to supply the necessary energy to overcome the aforementioned interparticulate forces are known as passive devices, whereas active devices use additional sources of energy.

One advantage of using a patient's inspiratory airflow as the primary source of energy is that such devices are breath actuated, which eliminates the need for the patient to synchronise the actuation and inspiration manoeuvre. The disadvantage of this approach is that current devices exhibit device-specific airflow resistance, which often necessitates a relatively high inspiratory effort [31] and may pose a challenge for patient populations suffering from obstructive airway diseases such as asthma or COPD, the elderly, or the very young [32]. The extent of lung deposition is also affected by the particular patient's inspiratory flow rate, which might result in a variance in the dose successfully administered [33]. Dose metering is another important aspect influencing the consistency of doses given by multidose inhalers. Unlike single-dose and multi-unit dose devices, which employ premetered powders packed into blisters or capsules, powder bed bulk multidose inhalers use powder reservoirs, which require the dose to be separated from the bulk material prior to actuation [34]. Powder flow qualities are critical for both types of devices, whether for correct dosing or completely emptying the single-dose container.

Due to the poor flow qualities of micronized powders, most formulations consist of physical blends of drug particles with larger (30-90 m) carrier particles such as lactose to facilitate deagglomeration and powder flow [35]. Given the aforementioned considerations, the ideal DPI would deliver an exact dose every time, regardless of a patient's state. Clinically, it may also be beneficial if the device is breath-actuated, simple and safe to use, has some form of control feedback mechanism (related to efficacy), and has an accurate dose counter. The dose counting mechanism is a standardised requirement that helps patients track whether doses have been provided correctly and when to replace the device [36].

DPI Devices available in International Market

As described in the previous section, the safety and efficacy of local and systemic dry powder inhalation therapies are influenced by the inhalation device and formulation attributes used. Numerous DPI devices have been developed and marketed over the last 50 years, and inhaler features have steadily improved. The first generation DPI devices, such as the Spinhaler (Fisons, Ipswich, UK) and Rotahaler® (Glaxo, London, UK), had poor aerosolization performance with relatively low levels of medication in the 1-5 m range, described as the fine particle fraction (FPF), of roughly 10% [37,38]. FPFs of more than 20% [39] are achievable with generation two DPI devices, such as the Handihaler® (Boehringer-Ingelheim, Ingelheim am Rhein, Germany).

Modern devices, such as the Genuair® (Almirall Sofotec GmbH, Bad Homburg v.d. Höhe, Germany), perform even better, producing FPFs of over 30% [40]. Similar considerations can be used for airflow resistance and total emitted dose (TED). Table 1 provides an overview of many commercially available dry powder inhalation systems.

Table 1: Commercially Available DPI

DPI – Brand Name	Drug	Company Name
Spinhaler	Sodium cromoglycate	Aventis
Rotahaler/DPhaler®	Salbutamol sulfate. Beclomethasone dipropionate	GSK/Cipla
Cyclohaler®/ Aerolizer®	Beclomethasone dipropionate, Budesonide, Formoterol hemifumarate, Ipratropium bromide, Salbutamol sulfate	Pharmachemie/ Novartis
Handihaler	Tiotropium,	Boehringer-Ingelheim
Turbuhaler	Budesonide, Formoterol hemifumarate	Astra Zeneca
Diskhaler®	Salmeterol xinafoate,	GSK

Several innovative dry powder inhalation devices have been approved in the previous years The TOBI® Podhaler® (Novartis, Basel, Switzerland) was approved in

Spring 2013 and provides a novel therapeutic alternative for individuals suffering from chronic Pseudomonas infections linked with cystic fibrosis. TOBI Tobramycin Inhalation Solution (TISTM) (Novartis, Basel, Switzerland) was already available in the United States in 1997 for use with the LC® Plus jet nebulizer (PARI Respiratory Equipment Inc., Midlothian, VA, USA).

The disadvantages of this regimen were the relatively long inhalation periods and the requirement to clean the nebulizer after each use, which may have increased the risk of lung infection from devices that were not thoroughly cleaned. Furthermore, nebulizers are fairly big, and this type requires a compressed air supply/generator to function. Furthermore, TIS must be refrigerated when stored [41, 42], or the product may degrade prior to usage. Given the aforementioned constraints, additional convenience for those patients who qualify for the TOBI Podhaler is required, as is a specific level of inspiratory performance and compliance, and increased adherence can be expected [43]. Much effort has been expended to identify alternative means of giving insulin that do not require the use of needles, which is believed to improve patient therapeutic comfort [44], as well as the therapy's safety, because the danger of hypoglycemic occurrences is lowered [45].

In 2014, Afrezza® (MannKind Corp., Valencia, CA, USA), using MannKind's proprietary TechnoSphere® technology delivered by the DreamboatTM inhaler, received FDA approval for the delivery of rapid acting recombinant insulin [46]. The majority of recently approved DPIs are for the administration of novel APIs or API combinations, particularly for the treatment of asthma and COPD

DPI for COPD

Genuair

The Genuair (Almirall Sofotec GmbH, Bad Homburg v.d. Höhe, Germany), marketed as Pressair® in the United States, is a multidose disposable inhalation device licenced in 2012 for the administration of aclidinium bromide [47], an antimuscarinic medication used to treat COPD. The design is similar to the Novolizer® (Novartis, Basel, Switzerland), its predecessor in development. It provides visual and audible feedback control mechanisms for priming and the proper inhalation manoeuvre. To prime the device, the patient must press and release a button on the device's back, causing the discharge of a single dose from a nonremovable cartridge. A control window turns green, indicating that the device has been primed and is ready for usage. An audible click signifies proper intake, and the control pane returns to red. Once the device has been primed, a trigger threshold mechanism prohibits the unintentional discharge of another dose. A cyclone separator [48] is used to deagglomerate particles.

In vitro testing with a five-stage multistage liquid impinger (MSLI) at a flow rate of 90 L/min (for 2.7 s) revealed an FPF of 40.35.6% (n=4) of the supplied dose. In 12 healthy participants, gamma scintigraphic studies revealed a lung deposition of 30.17.3% of the metered dosage. The average dose retained in the inhaler was 11.5%. Another study that looked at the peak inspiratory flow (PIF) using the device in patients with moderate to severe COPD found that the tested population could generate adequate PIF (92.015.4 L/min) to reliably inhale the complete dose. Furthermore, 97% of inhalation manoeuvres conducted with the Genuair were effective [49]. Chrystyn and Niederlaender reported an airflow-independent resistance of 0.031 kPa0.5 min/L and a constant delivery of small particle doses over an inspiratory flow rate range of 45-90 L/min, based on data from conference presentations. Because it is intended to be used on a regular basis for COPD treatment, the Genuair inhalation device has several feedback mechanisms to ensure patient compliance. The relatively low airflow resistance satisfies the needs of this patient population, and the FPF of around 40% is cutting-edge.

Breezhaler

Novartis (Basel, Switzerland) created the Breezhaler, which is marketed as Neohaler™ in the United States and is approved for the delivery of indacaterol (a long-acting -adrenergic medication) and glycopyrronium bromide (an anticholinergic agent), both of which are intended for the treatment of COPD. It is a single-dose, capsule-based inhaler, similar to the Handihaler (see Fig. 1).

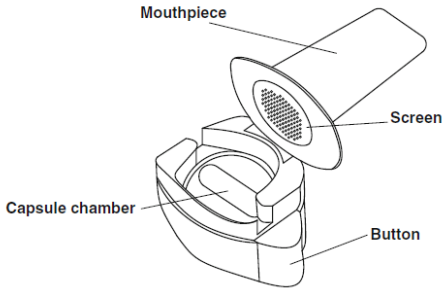

Figure 1. Schematic diagram of the Breezhaler

Before inhaling, the patient must tilt back the mouthpiece and place a capsule into the device, which must be perforated by pushing two buttons on both sides of the device [50]. When the capsule is pierced, an audible clicking sound indicates that the gadget is primed. The capsule generates a whirring noise when inhaled, which acts as a positive audio feedback control and shows that the powder is being inhaled. The patient is recommended to check for powder residues in the see-through capsule to ensure proper inhalation [51]. Because of its extremely low airflow resistance of 0.02 kPa 0.5 min/L, the Breezhaler reduces the effort required by patients to properly perform the inhaling manoeuvre, ensuring independence of aerosolization performance from the severity of COPD or age-related factors [52].

In vitro experiments using the next generation cascade impactor (NGI) coupled to a flow volume simulator, modelling a patient's breathing pattern, revealed an average FPF of 26.85.8% of the metered dose (150 g indacaterol). The measured MMAD was 3.20.22 m, and the emitted dose (ED) was 689.7% [53].

Genuair Vs Breezhaler

The Breezhaler has reduced airflow resistance than Genuair, which may promote compliance and thus safety

in COPD therapy. A clinical investigation was done to assess patient choice and satisfaction, as well as the convenience of use of both inhalers [54], but no results have been published too far. As a result, it is uncertain if the lower observed resistance may be directly translated into an overall therapeutic advantage. Control feedback devices, both audible and visible, ensure that the dose was properly primed and inhaled. Because the device is built as a single unit dose device, there is no requirement for a dose metering mechanism, making the delivery system more resilient when used correctly and less expensive to build. Carrying the device and blister packs separately, on the other hand, may appear to be an additional hardship to some patients, particularly while travelling.

Antibiotic DPI

Podhaler

The Podhaler, commonly known as the T-326 inhaler, is intended for use with Tobramycin Inhalation Powder (TIPTM) [55]. TIP is a particle-engineered tobramycin formulation developed by an emulsion-based spray drying method and based on the PulmoSphere® technology. Tobramycin and calcium chloride are mixed into the outer phase of a water-based emulsion containing perfluorooctyl bromide (perflubron) and distearoylphosphatidylcholine. Following spray drying, water and perflubron are removed, resulting in extremely porous particles (see Fig. 2) with drug loads as high as 90% w/w [56]. TIP has excellent flow and aerosolization capabilities and may be manufactured without the need of carrier particles. Due to the large dose of tobramycin required to provide effective therapy, a high drug load is required to keep the amount of powder to be inhaled low.

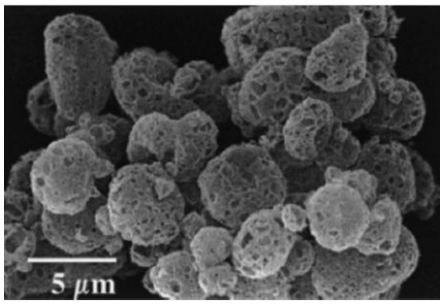

Figure 2. SEM image of PulmoSphere particles.

The Podhaler is a capsule-based passive single-unit dose inhaler based on the Turbospin® technology (PH&T, Milan, Italy). The patient must remove the mouthpiece, insert a TIP capsule, and then reinstall the mouthpiece to prime the device for inhalation. The capsule is pierced twice by a staple by squeezing a plunger on the bottom end of the device (see Fig. 3).

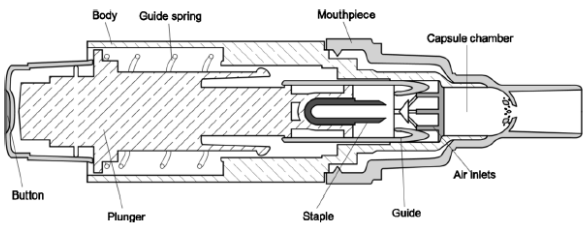

Figure 3. Cross-sectional view of the Podhaler device.

During inhalation, air is pulled through tangential holes in the capsule chamber, causing vortical motion and effective powder release, aerosolization, and entrainment [57]. The low airflow resistance of around 0.025 kPa0.5 min/L [58] and an optimised capsule filling capacity let most patients perform the inhalation manoeuvre successfully.

In vitro tests with the NGI at a pressure drop of 5 kPa and a flow rate of 85 L/min revealed a fine particle dosage of 13 mg. TIP capsules contain 28 mg tobramycin. Emitted doses at 40, 60, and 85 L/min airflow rates were found to be 93.5, 102, and 103.2% of the nominal label specified dose, respectively [58].

Because cystic fibrosis patients have similar issues during inspiration as COPD patients, reducing airflow resistance is critical for their compliance. As previously stated, employing TIP instead of TIS saves time and lowers the danger of patient infection from using an ineffectively cleaned nebulizer. Overall, the TOBI dry powder inhalation device is likely to be extremely beneficial for cystic fibrosis patients who have chronic *Pseudomonas* infections and are not being treated in a hospital setting.

DPI for Asthma Management

NEXThaler®

The NEXThaler (Chiesi Farmaceutici, Parma, Italy) is a multidose disposable passive DPI device licenced for the administration of formoterol fumarate and beclomethasone dipropionate. A desiccant, which is placed adjacent to the powder reservoir and separated by a semipermeable membrane, protects the dry powder formulation from external influences such as humidity in this device. A chamfer on the reservoir's front edge ensures that the powder is poured consistently into the dosing cup. This procedure is said to enhance dosage reproducibility [59]. The patient must first open the mouthpiece cover in order to prime the device. When the mouthpiece cover is closed [60], the integrated dose counter advances, but only if the metered dose has been breathed. When the breath actuation system detects an inspiratory flow corresponding to a pressure decrease of 1.5 kPa, the dose is released. The inspiratory flow resistance of 0.036 kPa0.5 min/L is intermediate, requiring an inspirational effort equivalent to Diskus® or Turbuhaler® inhalation. In vitro tests with the NGI at flow rates of 30 and 90 L/min demonstrate significant FPFs of 54.5 and 67.6%, respectively [61].

Though the NEXThaler device is probably the easiest to use in this segment, it has audible and visible feedback control features that indicate that the dose was correctly breathed. It's possible that a more visible control mechanism would have been preferable, because the patient needs to know how many dosages are left before and after inhalation. This visual impairment could pose a safety risk, especially in elderly patients. Because individuals utilising this inhaler may have reduced inspiratory capacities, a lower airflow resistance would be preferable. However, keep in mind that FPFs of more than 50% are a significant improvement over earlier DPI models.

Conix™

The Conix drug delivery platform (3M, St. Paul, MN, USA) comes in single-dose reusable, single-dose disposable, and multidose DPI configurations. A reverse cyclone is used to deagglomerate the powder composition. When activated, air and powder enter a conic chamber to form a free vortex. In contrast to a traditional cyclone separator, the bottom of the chamber is closed, causing the vortex to reverse the flow and create a second vortex in the centre that leaves via an aperture in the lid (see Fig. 4). This design is said to yield relatively high vortex velocities, resulting in efficient deagglomeration [62]. The cyclone retains carrier particles, decreasing the amount of powder that enters the patient's neck or upper airways [63].

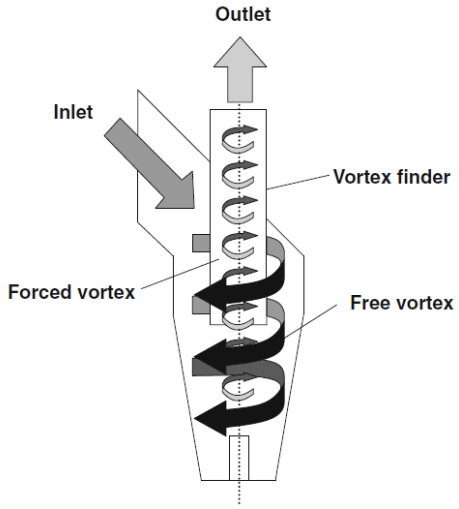

Figure 4. Schematic of the reverse cyclone technology used in the Conix device

In vitro tests employing an Andersen cascade impactor to aerosolize salbutamol powder formulations taken from the Accuhaler® (GSK, Brentford, UK) show an FPF of 85% and an ED of little more than 60%. The retention of carrier particles within the reverse cyclone separator is responsible for the high FPF. This powder retention is not a concern for a single-dose disposable unit; however, this type of carrier particle retention would be regarded harmful to the performance of a multidose type device.

Disposable Single-Use DPI

Most DPI devices are developed and marketed for the treatment of chronic airway diseases such as COPD and asthma, and they are optimised in terms of cost effectiveness as well as patient compliance and adherence to their routine medication. Aside from these well-established applications, DPIs are also a viable alternative for therapeutic or prophylactic interventions that may necessitate less frequent drug administration [64-66]. The TwinCaps® inhaler (Hovione, Loures, Portugal) was the first disposable single-use DPI device to be certified for the Japanese market in 2010. It is used to administer laninamivir, a new neuramidase inhibitor suggested for the treatment and prevention of influenza A and B virus infections. Patients with other infectious airway conditions, such as cystic fibrosis-related Pseudomonas infections or pulmonary aspergillosis, may benefit from disposable, rather than reusable, DPIs or nebulizers to reduce the risk of repeated infections. Similar considerations could be used to inhaled cancer therapy, reducing the possibility of unintentional exposure to highly cytotoxic medicines.

Dry powder formulations provide a noninvasive means of distribution as well as increased storage and transit stability. Another potential application for disposable DPIs is in emergency medicine. The FDA and European Medicines Agency (EMA) approval of the Staccato® device (Alexza, Mountain View, CA, USA) in 2012/2013 shows the practicality of this concept, despite the fact that it is not exactly a dry powder inhaler. It has been approved for the administration of loxapine, a dibenzoxapine antipsychotic medication used to treat agitation associated with acute schizophrenia episodes and bipolar I disorders. Other potential rescue medicine applications include acute pain control, migraine [67], and Parkinson's illness [68].

As previously stated in this section, single-use disposable DPIs must meet different specifications than reusable DPIs. However, the need for an effective dose measuring system is ruled out. Because the disposable DPI can be packaged and sealed, it is not exposed to direct environmental conditions such as humidity, and thus there may be no need to ensure a high level of drug protection within the DPI. Because patients who may use disposable DPIs are unlikely to be familiar with medical inhalation devices, it is preferable to maintain device operation as easy as feasible. Control feedback systems that are visible or audible would be extremely beneficial to naive patients. Of course, disposable devices must meet all of the standards for safe therapy, such as dose precision and repeatability.

Other Notable Devices

The ResQhalerTM (Aespira Ltd., Moshav Shdema, Israel) is a disposable, breath-actuated dry powder inhaler with audible control feedback. It makes use of the company's patented ActiveMesh® technology. Dry powder formulations are housed in a mesh-like box that releases particles in the respirable range when hitting the container with one's breath [69].

TrivAirTM (Trimel Pharmaceuticals, Mississauga, Canada), formerly DirectHalerTM, is a disposable dry powder inhaler for pulmonary and nasal administration. It is made up of a U-shaped inhaler tube with a corrugated bend that acts as a deagglomeration zone. Trimel began a phase II clinical trial of salbutamol sulphate in patients with intermittent or persistent moderate asthma in 2010. This trial's status is uncertain [70].

The CricketTM inhaler (MannKind Corp., Valencia, CA, USA) is a single-use disposable variant of the Dreamboat inhaler[71].

Occoris® (Team Consulting, Cambridge, UK) is an active powder aerosolization engine that may be used in single dose reusable and disposable inhalers as well as multi dose inhalers. It is intended to aerosolize unformulated powders, and the manufacturer emphasises the device's high performance while being inexpensive [72].

Conclusion

Dry powder inhalation has become widely available over the last five decades and has established a vital role in the treatment of respiratory disorders. The discipline has grown to cover not just local therapy for obstructive pulmonary disease, but also systemic distribution of drugs that require parenteral administration or regimens that may require a rapid commencement for the desired therapeutic effect. The availability of dependable, low-cost, and convenient single-use dry powder inhalation devices may influence the development of future immunisation tactics, and it is likely to become increasingly essential in the treatment of respiratory infections.

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