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Single-use disposable dry powder inhalers for pulmonary drug delivery

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Importance of the field: The understanding of pulmonary drug delivery and thus its utilization for medical purposes has remarkably advanced over the last decades. It has been recognized that this route of administration offers many advantages and several drug delivery systems have been developed accordingly. Thereby, single-use disposable dry powder inhalers may be considered an economically and therapeutically valuable option for both local and systemic administration of drugs to treat a variety of different disease states.

Areas covered in this review/What the reader will gain: This review highlights the required characteristics and potential applications of single-use disposable dry powder inhalers considering advantages as well as limitations of these drug delivery devices. Until now, such drug delivery systems have not become widely accepted. Several devices are available or under development and a few products have reached or completed the clinical phase, but none of them have received market authorization as yet.

Take home message: Recent advances in formulation and device design, however, can be considered encouraging and should eventually lead to a wider establishment of single-use disposable dry powder inhalers in pulmonary drug delivery.

Keywords: device, disposable, dry powder inhalation, single-use

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1. Introduction

During the past decades, inhalation aerosols have been widely used for medical purposes. The increasing occurrence of asthma and chronic obstructive pulmonary disease (COPD) has promoted the development of drug delivery systems for drug administration to the lung [1]. Beside the management of asthma and COPD, such aerosol delivery systems are also used or evaluated for other local applications of drugs to treat pulmonary infections [2] and lung cancer [3] and to provoke immune response [4]. Using this mode of drug delivery has the particular benefit that the drug is directly delivered to the target area. As a consequence, drug doses can generally be reduced and systemic side effects minimized. It has also been recognized that the pulmonary route can not only be used for local application of drugs but also effectively deliver drugs for systemic treatment of different disease states [5,6]. The alveolar tissue in the lung provides a large surface area, is effectively perfused with blood, has only little drug-metabolizing and efflux transporter activities and represents only a minimal physical barrier between airspace and bloodstream. These characteristics enable rapid absorption into the systemic circulation without the production of metabolites and a convenient, non-invasive mode of administering substances which show no, poor or variable systemic bioavailability when applied via the peroral route, for example, macromolecules. Drug administration via the

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Article highlights.

- Understanding the key requirements and opportunities for dry powder inhalers (DPIs).
- Learning about the specific issues with single-use DPIs.
- Discussion of current and potential applications for single-use DPIs.
- Overview of early and late stage development projects, devices and technology platforms.

This box summarizes key points contained in the article.

pulmonary route is, therefore, increasingly applied or considered as an option for a variety of diseases such as pain relief [7,8], diabetes [9] and disorders of the CNS [10]. **Table 1** summarizes the current and future indications of drug application to the lungs.

Different delivery systems are available for pulmonary drug delivery, for example, large and small volume nebulizers, pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). These systems were primarily developed for the treatment of asthma and COPD. The nature of these diseases generally requires a chronic and frequent medication. Currently marketed inhalers are consequently intended for multiple (daily) use. Nebulizers are advantageously prescribed for patients who are unable to achieve sufficient inspiratory flow (children, elderly patients and patients with severe airway obstruction or intubation) [11]. However, routine use of nebulizers is limited by disadvantages such as complexity and consequently high cost, low drug delivery efficiency as well as strict cleaning requirements to avoid microbial contamination of the device and infection of patients with pathogens [12,13]. The most commonly used systems are pMDIs and DPIs which can be applied for a broad population of patients as routine medication [14]. Despite certain disadvantages including difficult breath-coordination and cold Freon effect (discontinued inhalation due to a chill effect caused by quickly evaporating propellant), pMDIs still take the major share of the market in Europe (two-thirds of unit sales in 2004) [15]. This is mainly attributed to their simple press-and-breathe function (simplicity), ease of substitution (similarity) and several cost benefits. DPIs avoid the breath-coordination and the cold Freon issue, but require, at least in case of passive inhalers, a minimum inspiratory flow rate [11]. Also, DPIs are not easy to formulate and manufacture and the device development needs considerable expert input. However, DPI products feature some major advantages: combination products can be developed more easily, the formulation prepared as dry powder generally leads to enhanced stability of the drug product and high doses of drug can be administered [16]. There is no doubt that modern multiple-use devices are the most cost-effective choice for the treatment of asthma and COPD. However, the treatment of other diseases often requires less frequent, transient or even a once-only application of the medicament limiting the cost-effectiveness of multiple-use devices. Also, occasional use, such as use in hospitals, may be favorable with single-use disposable devices. Thus, these devices can represent a valuable alternative to multiple-use devices. It is obvious that a simple adaptation of rather complex nebulizers as well as pMDIs to single-use devices is difficult. Dry powder inhalation systems, however, can easily be adjusted to meet the requirements of single-use inhalation devices. It is the intention of this review to highlight specific requirements for single-use DPIs and show how these can be implemented. Current and potential future applications of single-use disposable DPIs are evaluated. In addition, currently marketed or single-use inhalers under development are reviewed considering advantages as well as limitations of such drug delivery devices.

2. Requirements for single-use dry powder inhalers

Like other DPI types, single-use DPIs should meet the general requirements for inhalation drug products regarding clinical efficacy, device reliability, patient compliance and cost-effectiveness. Due to the disposable design, some desirable features of multiple-use DPIs can be disregarded. A dose-metering mechanism as well as a dose counter is not necessary. In addition, the inhaler need not be designed to be refillable. However, there may be several specific requirements for disposable DPIs related to their potential field of application and economic success. For the treatment of disease states that require continuous and frequent medication, single-use devices are assumed to be not competitive, both from an economic and environmental point of view. In an age of scarce resources and environmental pollution, especially the latter needs to be considered as providing a rationale for the utilization of single-use devices. It is very likely that single-use DPIs will be used for acute or transient disease state therapy as well as for vaccination. As a consequence, such inhalers will predominantly be used by patients or subjects not familiar with inhaled medicines. A self-explanatory, intuitive functionality that preferably requires minimal training represents the major prerequisite for each single-use DPI. Ideally, the ease of application is facilitated by user instructions supplied with the device or on each individual inhaler package. To meet this requirement, the device should be designed to be as simple as possible. This simplicity also facilitates the achievement of extensive cost-effectiveness through inexpensive manufacturing and assembly and cost-effective development of the device. With regard to economic competitiveness, it is furthermore of particular interest to use a reliable and low-cost mode of powder filling. Although devices utilizing active powder dispersion principles are increasingly considered as an alternative to passive devices, it is rather questionable whether single-use active devices can economically and environmentally compete against their passive counterparts. Finally, the inhalation system should enable the application of different drugs and doses. Important

Table 1. An overview of current and potential future applications for single-use DPIs.

Local	Systemic
Acute asthma (as quick relief medication only)	Acute pain
Pulmonary infections	Migraine
Vaccination	Anorexia
Lung cancer	Acute agitation
	Erectile dysfunction
	Nausea and vomiting
	Smoking cessation (as quick relief medication only)

DPI: Dry powder inhaler.

characteristics, which are desirable for single-use inhalers, are summarized below:

- Precise and consistent dose delivery over a wide range of inspiratory flow rates
- Moisture protection of the device as a whole to enable stability of the formulation in the device and uniform dose delivery during the period of application
- Appropriate drug formulation to target the intended site of action
- Simple to use and easy to teach, preferably self-explaining functionality
- Convenient to carry
- Audible and/or visual indication of successful inhalation
- Maximum drug delivery to the target area and minimum drug losses in the device and the oropharynx
- Suitability for different drugs and doses
- Efficient and reliable mode of powder filling
- Low number of device parts, which can inexpensively be produced and assembled.

3. Current and potential future applications of single-use dry powder inhalers

3.1 Local delivery of drugs

As briefly discussed above, drug delivery by the pulmonary route using single-use inhalers can offer several advantages compared to other modes of drug administration. The most important advantage is related to the drug delivery to the lung tissue, when local action of the drug is desired. Considering the above discussed requirements, the simplest application of single-use DPIs would be the treatment of acute asthma, where the inhaler would serve the patient as an emergency medication. Disadvantages of commonly used pMDIs, which are difficult to operate even under normal conditions, could be avoided. As most DPIs rely on the patient's inspiratory effort while the inspiratory flow rate during an asthma attack is substantially decreased, sufficient drug delivery to the lower airways must be ensured even under these conditions. Thus, both the device and the powder formulation of the single-use inhalation system need to be designed to effectively deliver the drug at low inspiratory flow rates [17]. In acute asthma, it is frequently the case that multiple doses are needed for symptom relief. Consequently, the value of an application of single-use DPIs for this purpose might be limited. A sound rationale, considering the environmental impact compared to alternative options, is, therefore, needed to justify this application.

Single-use DPIs may also represent a valuable alternative in the treatment of pulmonary infections which generally require the delivery of high doses of antibiotics in the range of a few up to several hundred milligrams. Nebulization represents the standard method for local delivery of anti-infectives and has successfully been used in the treatment of various infections, for example, pneumonia in cystic fibrosis and pulmonary aspergillosis [18,19]. Both dry powder inhalation and nebulization enable the delivery of high doses of anti-infectives directly to the place of infection. It is important to recognize that current DPIs are limited regarding the maximum possible dose of a single inhalation. Nevertheless, new developments in device design successfully focused on the effective delivery of high dosed antibiotics [20,21]. With the neuraminidase inhibitor zanamivir (Relenza™, GlaxoSmithKline), the first DPI product became available for the treatment and post-exposure prophylaxis of influenza A and B [22]. The powder is dispersed with the Diskhaler™, a single-dose, multiple-use DPI. The risk of microbial re-infection or cross-contamination caused by contaminated inhalation device is inherent in multiple-use DPIs as well as in nebulizers [13]. To minimize this risk, measures such as disposable face masks or mouthpieces and mechanisms preventing exhalation into the device need to be taken, all of which are redundant when using single-use disposable DPIs. Furthermore, better patient compliance may be obtained through one or a few single powder inhalations rather than time-consuming inhalation by nebulization. Compared to the systemic application of anti-infective drugs, usually lower doses are possible and systemic side effects are less likely to occur.

The local treatment of lung carcinomas represents another promising application of single-use DPIs. In addition to the already discussed advantages of regional drug delivery, inhalation allows for a non-invasive 'needle-free' application of chemotherapeutics and may, in conjunction with less systemic side effects, further improve patient compliance [23]. The development and use of inhaled chemotherapeutic agents has been limited, however, mainly due to the hazard of severe pulmonary toxicity. In this regard, it also has to be recognized that the target area in the lung may differ depending on the kind of lung carcinoma, for example, primary lung cancer in the central airways and bronchial–alveolar carcinoma in the more peripheral lung region [3]. Appropriate device design and formulation are, therefore, needed to specifically target the desired area of deposition and to avoid local side effects in the oropharyngeal region. Furthermore, conventionally applied nebulizers bear the risk of occupational exposure of chemotherapeutics to healthcare staff. As a consequence, the

treatment needs to be executed in special rooms equipped with air-cleaning systems [24]. When considering the utilization of a single-use DPI, which in the simplest case involves opening, inhaling and discarding, it becomes obvious that with this mode of operation the risk of environmental contamination could be reduced. It even appears conceivable to translocate part of the chemotherapy to the patients' home resulting in generally lower cost and better patient compliance.

Finally, inhaled vaccination is increasingly considered as a valuable alternative to injected vaccines. The rationale for vaccination via aerosols is based on several advantages [25]:

- Many vaccines prevent respiratory infections.
- Transmission of blood-borne diseases, for example, hepatitis B and C and HIV, by inappropriate use and handling of used cannulas is avoided.
- No strategy for collection and disposal of used injection materials is required.
- Severe adverse events due to inappropriately stored, contaminated multi-dose vials are avoided [26].
- Inhalation addresses needle fear, especially in children.
- A more potent local immune response can be obtained for a variety of antigens.
- In young children, the known interference of persisting maternal antibodies with subcutaneously applied vaccines could be prevented.
- Until now, inhaled vaccination represents an untapped market opportunity.

Immunization via inhalation has been shown to be effective. Tent-exposure systems and nebulizers were successfully used for measles vaccination [25,27]. Furthermore, the WHO explores the possibility of inhaled measles vaccination for application in mass immunization campaigns [28]. Most attention is paid to the nebulization of currently available liquid formulations for injection, whereas the evaluation of dry powder formulations is considered for later trials [25]. The utilization of inhaled immunization against bioterrorism agents, for example, *Francisella tularensis*, is also being explored [29]. In this regard, it seems feasible to use the pulmonary route not only for prophylactic measures but also for the application of rescue medications such as antitoxins. These applications provide excellent opportunities for the utilization of single-use disposable DPIs, as transient and infrequent treatments are necessary and hygienic requirements are adequately addressed. However, little information is so far available on the effectiveness of vaccines when delivered to patients with compromised lung capacity (such as in asthma and COPD) or other inflammatory lung diseases with changed mucosa morphology.

3.2 Systemic delivery of drugs

Some general prerequisites need to be defined before potential applications of single-use DPIs for systemic drug delivery can be discussed. The most important is to target the respiratory tissue of the lung, that is, alveoli and respiratory bronchioles, in a way that enable effective and reproducible drug deposition and absorption [30]. In addition, the systemic treatment of diseases via the lung often requires a higher dosage of the drug compared to the conventional local therapies. Sophisticated devices and formulations are consequently needed to ensure the delivery of high drug masses with high efficiency and dose reproducibility. Several single-use disposable DPIs (refer to Section 4 of this review) and formulation approaches [31,32] are available to achieve these goals. Delivering drugs to the systemic circulation via the respiratory lung tissue generally offers a lot of potential advantages, especially in comparison to the peroral route of drug administration (**Table 2**). Considering these advantages, the utilization of single-use disposable DPIs is specifically beneficial for the administration of two particular categories of drugs. The first category contains molecules with no, poor or variable peroral bioavailability, that is, drugs susceptible to the effect of ingestion, gastrointestinal inactivation or metabolism, first-pass elimination and molecules exhibiting low permeability. The second category is represented by therapeutics requiring a fast onset of action. Preferably, drug inhalation for both categories of diseases is limited to one or only a few inhalations in order to keep treatment and device costs low.

Peptides and proteins are prominent candidates for systemic delivery via the lung [5,6] and a variety of molecules has been investigated for such applications [6,33]. In general, macromolecules cannot be administered via the gastrointestinal tract but require a parenteral application, mostly by injection. The utilization of single-use DPIs may, therefore, represent a cost-effective and convenient alternative. A major obstacle for this approach might be the need for a stable dry powder formulation, as large molecules and their formulations are often moisture-sensitive and hence susceptible to instabilities [34]. However, as already described in Section 2 of this review, in disposable devices the powder can be protected by an appropriate packaging of the device itself. Limitations of systemic delivery of macromolecules via the lung may rather be expected from absorption and permeation barriers as well as elimination mechanisms at the respiratory tissue [35]. These potential constraints, however, must be considered anyway and are not specific to single-use disposable devices.

Immediate medication and fast onset of drug action are desired for many therapies. Besides injection, which is typically only available in clinical environments, other approaches such as buccal or nasal administration are used to avoid the lag time of drug action inherent to peroral medications. The specific characteristics of the respiratory lung tissue enable rapid and extensive drug absorption and delivery to the blood (**Table 2**) resulting in pharmacokinetic profiles comparable to injections, high absolute bioavailability [36] and fast systemic drug action [37]. Thus, inhalation in general addresses the requirements for such therapies, whereas single-use disposable DPIs offer the additional advantage of immediate

Table 2. Specific characteristics of the respiratory lung tissue and resulting advantages.

Characteristics	Potential advantage
Large absorptive surface area Minimal barrier between air and blood	Absorption and systemic bioavailability of drugs with low permeability including large molecules (< 30,000 Da)
Effective blood perfusion Absorption directly into the systemic circulation	Rapid systemic bioavailability and avoidance of first-pass effect
Little drug-metabolizing and efflux transporter activities Absence of aggressive media such as gastric fluid	Systemic bioavailability due to little loss by gastrointestinal inactivation or metabolism
Absence of interindividual differences in qualitative and quantitative metabolisms due to missing flora and fauna	Reproducible systemic bioavailability

availability and unrestricted applicability regarding time and location of drug administration, especially compared to nebulizers. Based on these considerations, the following potential applications for single-use disposable DPIs can be identified (references indicate work on dry powder formulations):

- Cancer breakthrough and postoperative pain: opioids [38]
- Treatment of migraine attacks: dihydroergotamine and triptans [39]
- Acute agitation in schizophrenia and bipolar disorder: loxapine (refer to Section 4 of this review)
- Cancer- or AIDS-associated anorexia: cannabinoids [40]
- Chemotherapy-induced nausea and vomiting: antiemetics, for example, 5-HT_3 antagonists
- Smoking cessation: nicotine (as quick relief medication only)
- Erectile dysfunction: PDE5 inhibitors and apomorphine [41].

4. Single-use dry powder inhalation devices and technology platforms

4.1 Solovent

BD's Solovent (Becton, Dickinson and Co.) system was primarily developed to deliver vaccines to the lung or nasal cavity. The modular system consists of a standard syringe, a proprietary, powder-containing cartridge and an optional diffuser (**Figure 1**). A powder-containing plastic capsule equipped with pressure-activated rupturable films is held within two plastic parts forming a housing. The depression of the syringe plunger generates an air flow through the cartridge causing the rupturable films to burst and the powder to disperse. This system can be used for both pulmonary and nasal administration of powders [42]. Cascade impaction analyses of dry powder salbutamol formulations have shown the device to generate respirable fractions of up to 35%. Although the concept of this device was proven for pulmonary delivery *in vitro*, it has been studied more intensively for nasal administration of vaccines, which is beyond the scope of this review [4,43,44]. Nevertheless, this single-use disposable delivery concept is believed to represent a promising option for pulmonary applications, too.

4.2 TwinCaps®

The TwinCaps®, developed by Hovione (Loures, Portugal), represents a special case of a single-use disposable DPI, because it is, other than most single-use disposable systems, not necessarily used as a single-dose inhaler. It consists of only two plastic components, a movable dose compartment and a non-movable inhaler body (**Figure 2**) [45]. The dose compartment contains up to two single doses which can be filled by standard industrial filling machines. After filling, the movable part is inserted into the non-movable inhaler body. In closed position, the inhaler body serves as protective housing to avoid environmental contamination of the powder dose. To start inhalation, the patient pushes the dose compartment sideways such that the first dose is in alignment with the mouthpiece of the inhaler. The patient's inspiration creates turbulent air flow inside the dose chamber and the inhalation channel which ensures powder release and de-agglomeration, similar to the operating principle of FlowCaps®, Hovione's first DPI development. For inhalation of the second dose, the dose compartment simply needs to be pushed the other direction until the dose is aligned with the mouthpiece.

Limited data are available regarding *in vitro* performance characteristics of the TwinCaps. A recent publication, comparing *in vitro* powder de-agglomeration in TwinCaps, HandiHaler™ (Boehringer-Ingelheim), and Diskus® (GlaxoSmithKline) using cascade impaction analysis along with computational fluid dynamics simulations, showed the highest dispersion energy to be present in the TwinCaps which also corresponded to the highest fine particle fraction based on the emitted dose [46]. It should, however, be noted that compared to the other devices the emitted fraction was substantially lower for the TwinCaps limiting its overall device efficiency.

The TwinCaps inhaler is licensed to Daiichi Sankyo Co. Ltd (Tokyo, Japan) and Biota Holdings Ltd (Victoria, Australia). These companies are currently co-developing the compound CS-8958 (laninamivir octanoate), a novel inhaled long-acting neuraminidase inhibitor to treat influenza virus infections. Various studies have shown the compound to be safe and effective against influenza types A and B as well as oseltamivir-resistant viruses [47-50]. In Phase I clinical trials, the treatment was shown to be safe and well tolerated, even in subjects with severe renal impairment [51,52]. Recently, Phase III clinical trials proved successful and a New Drug Application (NDA) has been filed in Japan for the compound CS-8958 which is delivered using the TwinCaps inhaler [53-55].

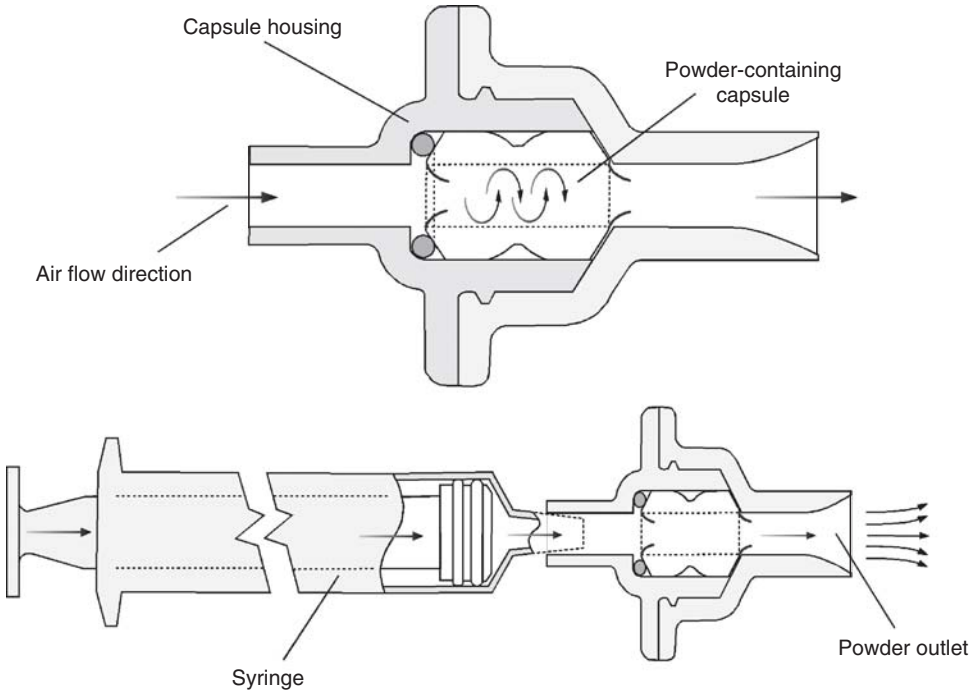

Figure 1. Solovent system: powder capsule including syringe (bottom), detailed view of powder capsule (top).
Modified from [42].

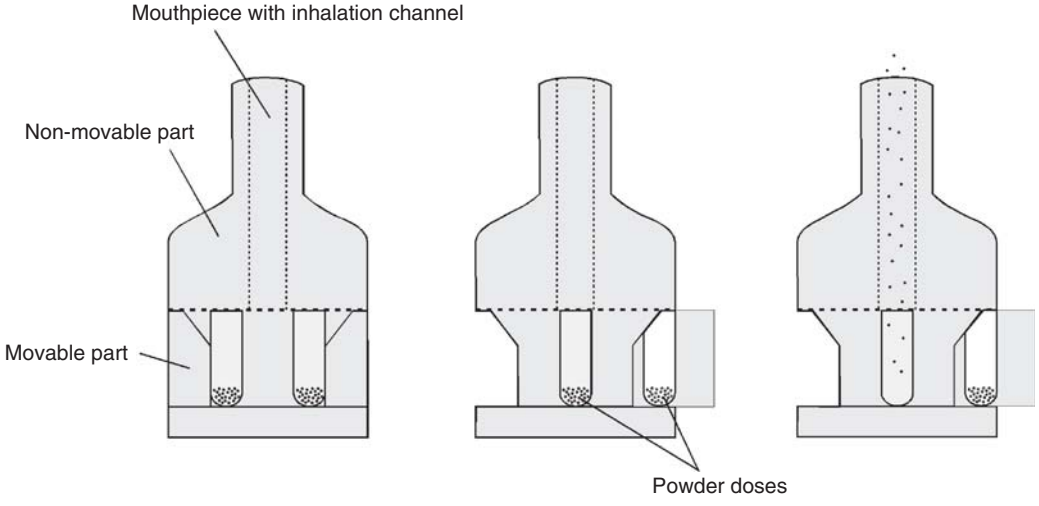

Figure 2. TwinCaps® DPI: as supplied (left), first dose loaded (middle), first dose during inhalation (right).

The most remarkable advantage of this new therapy option is that the long-acting compound is directly delivered to the area of action. As a consequence, only a single inhalation of the drug is necessary to effectively treat influenza infections making the treatment highly cost-efficient [48]. Compared to the existing medications, Relenza (GlaxoSmithKline) and Tamiflu® (Roche), less drug is needed and patient compliance can be improved through a very simple operation of the device and short treatment duration. In addition, the dose regimen and convenient use of the TwinCaps/CS-8958 combination might qualify the system also for prophylaxis of pandemic influenza.

4.3 3M Conix™

Based on the proprietary reverse-cyclone technology which was licensed to 3M by Cambridge Consultants Ltd, 3M offers

several designs of the Conix™ DPI technology [56,57]. The 3M Conix DPI is available as single-dose, both reloadable and disposable, and as multi-unit dose systems (**Figure 3**). On inhalation by the patient, inspired air entrains the powder formulation stored in a blister [58]. Air and powder laterally enter a cone-shaped cyclone chamber, where a vortex is established. The vortex creates comparably high velocities and de-agglomeration is accordingly obtained by collisions of particles with the cyclone wall or other particles, but also by particle shear. As the chamber is closed at the bottom, the air flow reverses, passes the incoming air flow and exits the chamber at the top. This mode of operation prevents large particles from being released which presumably contribute to reduced oropharyngeal drug deposition and higher respirable fractions. In an *in vitro* comparison of GSK's Diskus and a 3M Conix prototype device using the same salbutamol interactive mixture, lower throat and pre-separator depositions as well as higher fine particle fractions could be shown for the 3M Conix device [58]. However, the emitted fraction was only slightly above 60% which was not further discussed by the authors. Large, drug-loaded carrier particles retained in the cyclone chamber are a possible reason for this observation. A reduction of such residues by the application of carrier-free formulations and further device optimization could improve the cost-effectiveness of the promising Conix design concept.

4.4 Twincer®

This device basically consists of three plate-like plastic parts forming the air flow passages and a blister strip containing the powder formulation (**Figure 4**) [20]. The patient opens the blister before inhalation by pulling the folded cover foil. Now, the blister is connected to the powder channel and, on patient inspiration, the powder is entrained by air and conveyed to two parallel cylindrical chambers, also called air-classifiers. The tangentially arranged classifier inlets cause a vortex within the chambers ensuring particle break-up mainly by collisions of the particles with the classifier wall and other particles. By choosing an appropriate layout and dimension of the classifier outlet, the residence time of the powder and the size of particles leaving the classifier towards the mouthpiece can be controlled within certain limits. *In vitro* de-agglomeration experiments using micronized colistin sulfomethate have shown excellent, flow rate-independent de-agglomeration behavior even at high powder doses of 25 mg [20]. Even with 25 mg doses of micronized tobramycin, which is known to be difficult to disperse, acceptable respirable fractions of ~ 40% were obtained [59]. Also in this study, co-micronizing the tobramycin with different sugars remarkably increased the resulting fine particle fractions up to 50%. A further substantial increase in respirable fractions was obtained by the subsequent processing utilizing a novel, simple method for controlled agglomeration of micronized substances [60]. In addition, the utilization of sweeper particles (normally coarse lactose particles) has been shown to improve the performance of the Twincer® device by increasing emitted fractions [61].

The concept of the Twincer has also been proven *in vivo* [62-64]. Dry powder inhalation of colistin sulfomethate using the Twincer was shown to be well tolerated in healthy volunteers and cystic fibrosis patients without significant effects on FEV_1 or adverse events [62,64].

In summary, the concept of the Twincer enables effective powder dispersion and pulmonary drug delivery without the need for complex particle engineering and formulation techniques.

4.5 DirectHaler™

A very straightforward device platform, the DirectHaler™, was developed by Direct-Haler A/S (assets acquired by Trimel BioPharma SRL in 2009). The device resembles a drinking straw and consists of a U-shaped inhaler tube with a corrugated bend (**Figure 5**) [65]. A double cap is used to seal both ends of the inhaler tube. Powders that are not, or only marginally, susceptible to physical and chemical instabilites during storage and transportation can directly be filled into the tube. Sensitive formulations, however, can be filled into a special cap sealed with a laminate foil strip and thus protected from mechanical stress, light and moisture until the powder is released into the inhaler tube by removing the sealing. For inhalation, the patient uses one end of the tube as mouthpiece. The turbulent air flow formed within the tube during inhalation is claimed to generate turbulent whirls at the corrugated surfaces of the tube and to force the powder on the walls of the corrugations, from where it is gradually and completely released towards the mouthpiece [65]. Non-peer reviewed *in vitro* and *in vivo* data suggest that performance and safety characteristics are comparable to that of marketed inhalation systems [66]. Due to the very simple design of this device, cost of material and goods may be exceptionally competitive [67,68].

4.6 Aespironics' DryPod DPI technology platform

Aespironics Ltd is developing a single-use disposable DPI based on its proprietary ActiveMesh™ technology [69]. A unique feature of this technology is the packaging of the powder in a mesh compartment located on a reed or spring and the beating and vibration of this mesh package on inhalation by the patient. This action forces the powder agglomerates through the mesh holes, thereby releasing and de-agglomerating the powder at the same time. Two different embodiments of this technology are available, a credit card shaped and a whistle shaped inhaler (**Figure 6**) [70]. The credit card shaped inhaler uses a rotor to beat the mesh package, whereas the whistle-shaped embodiment uses a vibrating reed-like rocker. During application, the patient receives an audible feedback of successful inhalation by the beating action. Besides other concepts, the technology has already been presented as a potential delivery system for inhaled vaccines [71]. In an *in vitro* proof-of-concept study, the device prototype has been shown to effectively release and de-agglomerate micronized powders without the need for any additional excipients or special powder engineering [72].

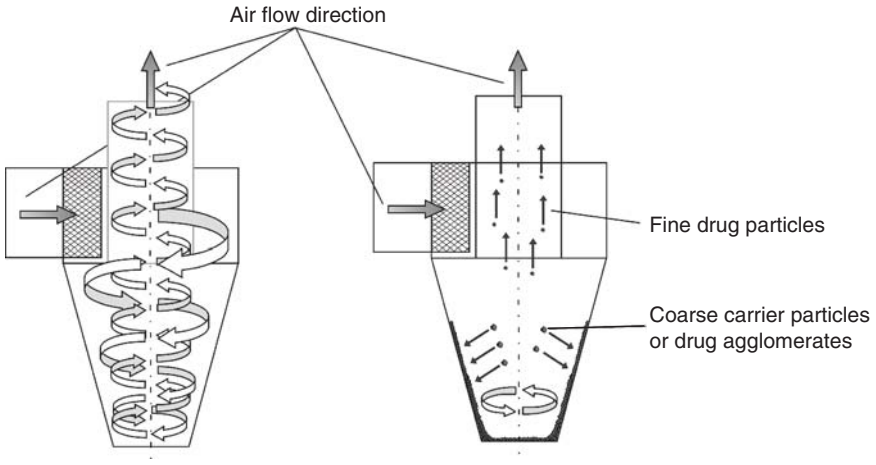

Figure 3. Principle of 3M Conix™ DPI technology: air flow path (left), particle path (right).
Modified from [58].

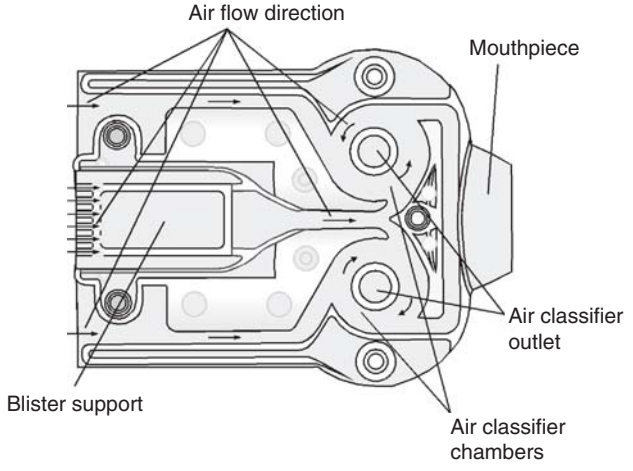

Figure 4. Twincer®: cross-sectional view from top (connection of air-classifiers to mouthpiece not shown).

Limited powder release was observed only at low air flow rates. However, appropriate countermeasures for device optimization were proposed. A smaller mesh hole size increased the amount of respirable particles and reduced the fraction of non-respirable agglomerates. The dispersion of powder doses of up to 3 mg resulted in acceptable fine particle fractions. Thus, Aespironics' DryPod DPI platform represents a promising concept for single-use applications.

4.7 Alexza Staccato®

Alexza's Staccato® system cannot be considered a DPI. Nevertheless, it is mentioned in this review as it represents an interesting single-use disposable inhalation system. Conventional powder formulations, however, cannot be used with this inhaler. The system comprises an active dispersion mechanism, which is not a bulk powder dispersion mechanism in the classical meaning. Pure drug is coated onto the stainless steel surface of a so-called heat package [73]. A plastic housing arranged around the heat package forms the inhalation channel. Once the patient starts inhaling, a breath sensor initiates a chemical reaction within the heat package causing instantaneous heat generation which leads to vaporization of the drug coating. The drug vapor follows the air flow and condenses into solid particles in a size range appropriate for efficient lung delivery.

The concept has been studied extensively both *in vitro* and *in vivo* and was first reported in 2004 showing its suitability to efficiently deliver aerosols of a variety of small molecules with mass median aerodynamic diameters ranging from ~ 1 to 3 µm [74]. Emitted doses were found to be in the range of 84 – 100% of the loaded dose. Interestingly, no thermal decomposition was observed despite the high temperatures of ~ 350°C used during the vaporization phase, which was attributed to the very short period that the drug is exposed to heat (~ 50 ms). These findings were further supported by data obtained from experiments with Staccato Loxapine showing that drug degradation is generally low and the performance of the system is comparably insensitive to changes in heating temperature and coating film thickness [73]. Another study revealed a highly consistent *in vitro* emission of drug from the Staccato system, independent of air flow rate and inhalation profile [75]. Furthermore, the oropharyngeal deposition determined by using a realistic geometry was shown to be consistently as low as 11% of the emitted dose within a range of flow rates from 15 to 80 l/min.

Animal studies showed injection-like pharmacokinetic profiles for different drugs [74,76] and pharmacodynamic effects almost immediately after inhalation [74]. Staccato Loxapine has been investigated in clinical studies for the treatment of acute agitation in schizophrenia and

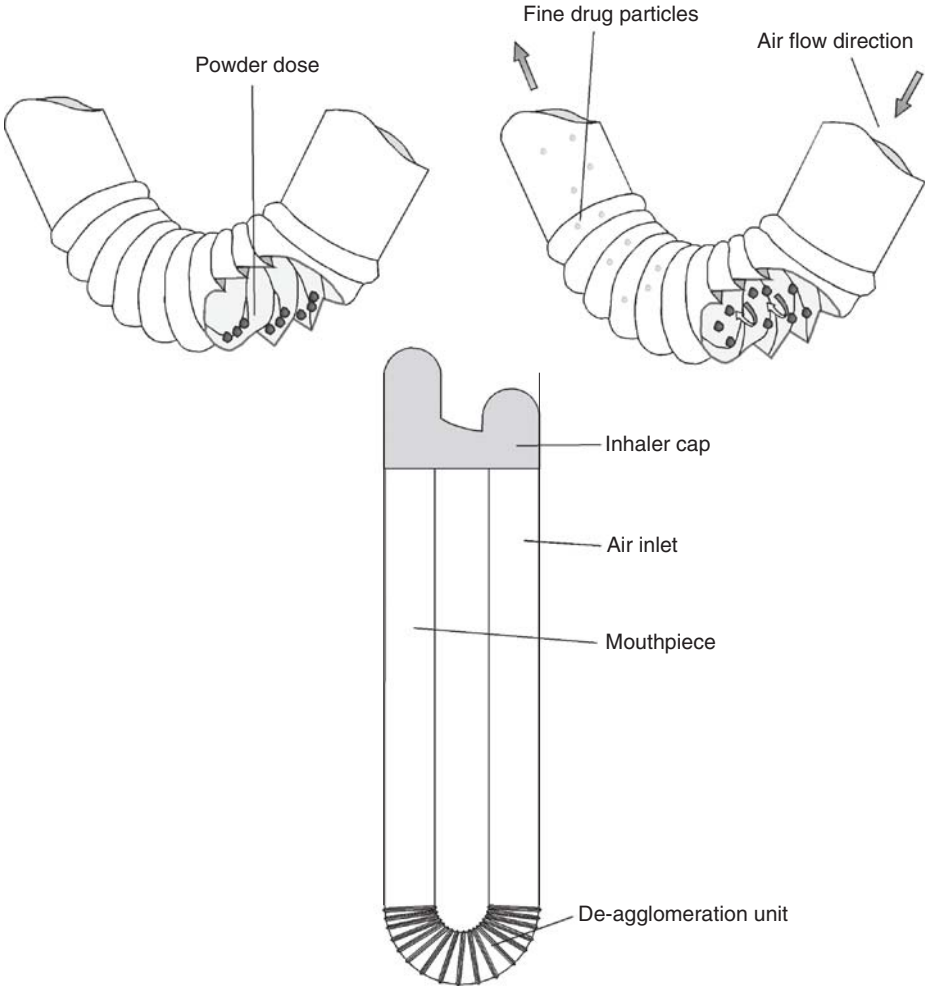

Figure 5. DirectHaler™: device with standard cap (bottom), detailed view of de-agglomeration unit (top left) during inhalation (top right).
Modified from [67].

bipolar disorder. The system was shown to rapidly deliver the drug to the systemic circulation and to be safe and well-tolerated by volunteers [10]. The efficacy of the system in conjunction with a fast onset of action was shown in placebo-controlled Phase II and III clinical trials [77]. An NDA has been submitted for the product to the FDA in December 2009 [78].

4.8 Further devices under development

This section summarizes information on further single-use disposable devices that are under development and that are available. Due to limited disclosure of information, it is – at this time – impossible to perform a fair and scientifically sound evaluation of these devices.

The S2™ Unit Dose DPI, embodied as a re-usable or disposable device, has been in the development portfolio of Vectura Group plc and was reported to enable the delivery of a variety of substances to the patients' lungs in high concentrations thereby requiring only minimal effort by the patient [79,80]. Furthermore, non-peer-reviewed preclinical and initial human experiments revealed that high fine particle fractions as well as highly efficient delivery to the deep lung can be obtained [80]. In the meantime, the S2 Unit Dose DPI disappeared from the company's official portfolio and the development of the disposable embodiment of this technology seems to be discontinued [81].

RPC Formatec GmbH offers the MonoHaler, a breath-actuated, blister-based single-dose DPI, available as a re-usable or disposable system (**Figure 7**) [82]. According to company information, important characteristics are easy blister filling and flexibility in blister size. It is further stated that high fine particle fractions are obtained with the MonoHaler.

Based on its existing delivery system MedTone®, MannKind Corp. provides a concept for a breath-actuated single-use disposable DPI [83].

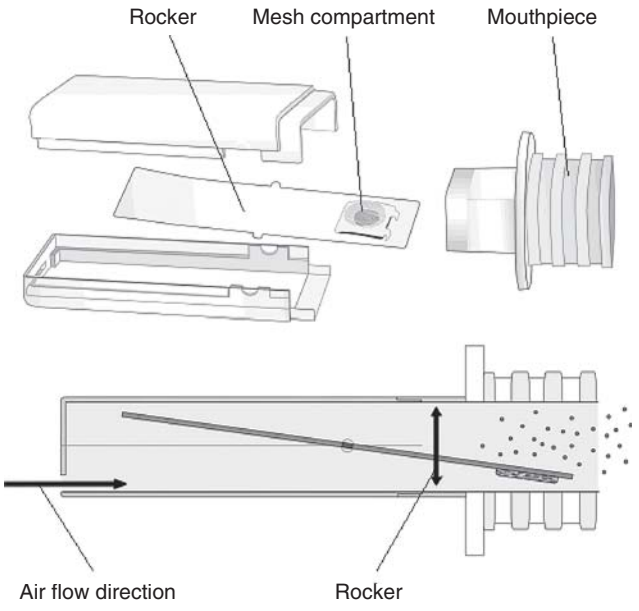

Figure 6. Aespironics DryPod DPI technology platform: whistle-shaped embodiment, exploded view (top), cross-sectional view during inhalation (bottom).

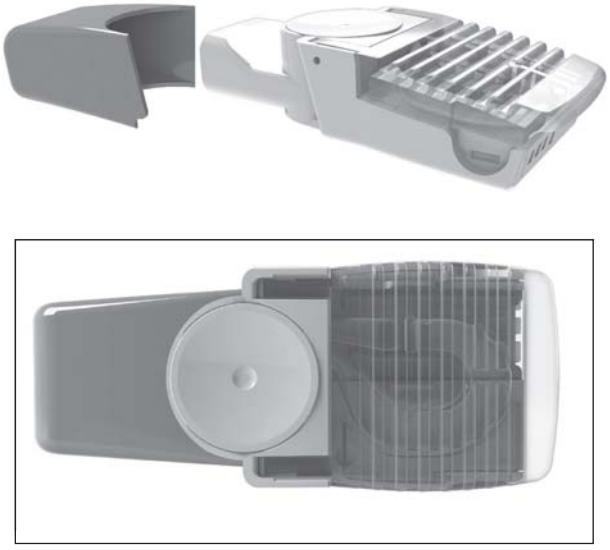

Figure 7. MonoHaler: perspective view (top), from top (bottom).

Another single-dose disposable DPI is offered by Manta Devices LLC. This concept is based on the company's Torus Dispersion Technology which utilizes air jets to de-agglomerate the powder dose contained in a toroidal chamber [84]. The company points out characteristics such as flexible dose loading with blended formulations or pure drug, user-friendliness including visible dosing confirmation and excellent environmental protection of the powder [85].

5. Conclusion

Specific requirements for single-use disposable DPIs were highlighted in this review. In contrast to the commonly used multiple-use DPIs, it is of vital importance to design the device as simple as possible allowing for a self-explaining functionality and cost-effective production. Further requirements are substantially the same as for multiple-use DPIs. As for other DPIs, several pharmaceutical and physiological aspects need to be taken into account when considering this mode of drug administration. To identify potential applications, however, it is particularly important to recognize specific advantages of single-use DPIs such as rapid applicability, ease of use and hygienic design as well as the intended therapy regimen. Based on these considerations, a wide range of future applications for both local and systemic drug delivery has been identified. Furthermore, a variety of single-use disposable DPIs has been discussed. Depending on their respective characteristics, it could be shown that the underlying concepts and technology platforms enable applications over a wide range of drug doses and for both local and systemic pulmonary drug delivery. All of these devices are still under development, but a few can be expected to reach the market in the near future.

6. Expert opinion

At the moment, it is obvious that single-use disposable dry DPIs do not represent a standard approach for drug delivery to the lung, although many promising products are under development. Explanations for this phenomenon are difficult to identify as this approach offers a broad variety of potential advantages and appropriate applications. A reason may be the fear to move away from established systems which have already been shown to provide adequate performance characteristics and proven to be safe and effective. Most of these systems are multiple-use systems which are particularly used to treat disease states such as asthma, COPD and to some extent pulmonary infections. With regard to chronic airway diseases, the clinical effectiveness and cost-efficiency of multiple-use systems cannot be doubted. Continuous and frequent medication is needed and, thus, multiple-use systems, in particular pMDIs and multiple-use DPIs, are qualified for such purposes.

However, for therapies requiring only a few or even a single treatment, the cost-efficiency of such devices may be questioned. The knowledge of pulmonary drug delivery substantially improved over the last 20 – 30 years and many new options for both local and systemic application of inhalation aerosols have been identified which in many cases require intermittent or single drug application. Single-use DPIs, being easy to use and rapidly applicable, hygienic, robust and cost-efficient, can, therefore, be considered a valuable option for such purposes. It seems plausible to consider these devices as an economically advantageous option for

applications where normally continuously working nebulizers are used, for example in clinical anti-infective therapy. Nebulizers are expensive, oftentimes exhibit inefficient drug delivery performance and require time-consuming set up by qualified staff as well as technical and anti-microbial maintenance. However, it must be recognized that a fair assessment of the potential financial advantages of single-use devices is difficult at the moment. In the absence of a specific product profile and an indication of the market size, the true value of a single-use disposable DPI cannot be assessed accurately. Systematic cost-effectiveness or cost-benefit analyses may help quantify the real economic value of single-use DPIs, thereby considering not only cost of goods and manufacturing, but also savings in patient healthcare due to better patient compliance, potential improvements in quality of life and the like.

It is worth pointing out that the advantages of single-use DPIs result from their inherently hygienic design and simple functionality. Based on these properties, such devices are perfectly suited for applications where it is required to apply medications to many untrained people and under difficult to control hygienic conditions. The inhalation of vaccines, especially for mass vaccination campaigns in developing countries, is, therefore, regarded as one of the most promising future applications of single-use DPIs. It is furthermore conceivable to use this approach as a rapid countermeasure in case of bioterrorism attacks or to provide soldiers with stand-by medications against biological or chemical weapons.

As highlighted in this review, many more potential applications represent an opportunity for single-use DPIs, but only few are considered to be realistic at the moment. More research in general and clinical research in particular is needed to show the true potential and facilitate the recognition of this drug delivery option.

Until now, several device platforms in different development stages are available. The adaptation of commonly used DPIs to meet the requirements for single-use applications does not seem to represent a remarkable challenge. Existing dispersion principles can easily be adapted to fit in single-use DPIs, as many companies offer different embodiments, including single-use concepts, for their inhaler platform. Similarly, the choice of an appropriate powder formulation, if required at all, seems to be no more challenging than for multiple-use DPIs. Common limitations of dry powder inhalation systems, however, need to be taken into account.

The Twincer is considered a promising concept for local drug delivery which is not limited to, but in particular suitable for, high dose applications in the anti-infective treatment of pulmonary infections such as pneumonia in cystic fibrosis. Results from clinical safety and pharmacokinetic studies with colistin sulfomethate are encouraging. However, studies on the clinical effectiveness, for example in the treatment of pneumonia in cystic fibrosis, would be desirable to establish a convenient and effective therapy option. The TwinCaps represents another promising concept for local pulmonary drug delivery. Limited *in vitro* data are available for this device; clinical investigations though enabled the filing of an NDA for the laninamivir octanoate–TwinCaps combination for the treatment of influenza virus infections.

In contrast to the concepts of Twincer and TwinCaps, the sophisticated design of the Staccato system primarily qualifies for systemic drug delivery via the lung. Its principle of drug vaporization and subsequent condensation leads to particle size distributions of the aerosol that enable effective drug delivery to the respiratory lung tissue and absorption to the systemic circulation. Extensive research on this device has been performed and published showing *in vitro* performance characteristics such as highly consistent emitted fractions, consistently low oropharyngeal deposition and excellent stability of the drug during vaporization. In addition, clinical investigations on Staccato Loxapine for the treatment of acute agitation in schizophrenia and bipolar disorder eventually led to the filing of an NDA. These three delivery platforms are deemed to be the most advanced and the best characterized single-use disposable devices. Whether or not these DPIs are going to be successfully commercialized remains to be answered.

A comprehensive discussion of the remaining concepts covered in this review is limited due to a lack of information in the public domain. The available data suggest that any of these single-use devices may be a suitable option for pulmonary drug delivery. At least, the design of these devices seems to meet the general requirements for single-use disposable DPIs. The Aespironics' DryPod DPI and the 3M Conix technology platforms showed acceptable *in vitro* de-agglomeration characteristics, but no more information has been published until now.

In conclusion, single-use disposable DPIs can be considered a valuable extension of existing drug delivery systems for pulmonary applications, not only from an economic point of view, but also with regard to patient compliance. In addition, a wide range of potential applications offers extensive market opportunities. Further evaluation of cost-efficiency as well as clinical research is required to enhance the recognition and acceptance of these drug delivery systems. It is expected that once the first single-use DPI product receives marketing authorization and proves successful in the market, the commercialization of such devices will be intensified.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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