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The role of disposable inhalers in pulmonary drug delivery

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Introduction: There is increasing interest in the pulmonary route for both local and systemically acting drugs, vaccines and diagnostics and new applications may require new inhaler technology to obtain the most therapeutically and/or cost-effective administration. Some of these new applications can benefit from the use of disposable inhalers.

Areas covered: Current trends in pulmonary drug delivery are presented in this review as well as the possible contribution of disposable inhalers to the improvement of pulmonary administration therein. Arguments in favour of disposable inhalers and the starting points for development of devices and their formulations are discussed. Also, a brief review of the state of the art regarding current disposable inhaler development is given.

Expert opinion: Prerequisites for the use of disposable inhalers, particularly dry powder inhalers, in applications such as childhood vaccination and for preventing or stopping pandemic outbreaks of highly infectious diseases (like influenza, bird flu, SARS) are that they are simple, cheap and effective. Not only do the devices have to be simple in design, but the drug formulations should also be cheap. This may require a different approach as the formulation may not need to be adapted to improve the inhaler must be designed to enhance formulation dispersion.

Keywords: disposable, dry powder inhaler, inhalation, nebuliser, single-dose, single-use


1. Introduction

Inhalation therapy has been the cornerstone in the management of asthma and chronic obstructive pulmonary disease (COPD) for more than half a century [1]. Pulmonary drug administration in the treatment of these diseases has the objectives to achieve local effects like suppressing inflammatory processes and provide relief in moments of bronchoconstriction. The advantages of pulmonary treatment of respiratory diseases are well known and include reduced systemic side effects and a rapid onset of action [2]. Local deposition on the site of action also results in higher local drug concentrations for much lower doses compared with systemic delivery [3]. Also for the maintenance treatment of cystic fibrosis (CF) [4,5] and the eradication of various pulmonary infectious diseases like pneumonia [6] and pulmonary aspergillosis [7], inhaled medication has become an interesting alternative [8].

More recently, other areas of interest for pulmonary drug delivery are being explored and the list of possible applications for this route of administration is rapidly growing and no longer confined to diseases that manifest locally in the respiratory tract [9,10]. Pulmonary application may be considered a good alternative for drugs that cannot be absorbed via the gastrointestinal tract effectively and are currently administered via injection. Drugs that can be absorbed after oral intake but suffer from rapid metabolism in the liver are now administered via a parenteral route. This requires the use of needles, and although developments in needle technology have reduced the burden of this invasive route of administration...
By their design, dry powder inhalers and jet nebulisers are most appropriate as disposable inhalers.

- Single-dose (rescue or relief) therapies, bronchial challenge tests and pulmonary vaccination are served best with disposable inhalers.
- Disposable inhalers eliminate the risk of bacterial resistance development in the administration device against the antibiotic(s) used.
- Hygroscopic drug formulations should not be administered with a reusable inhaler as moisture uptake by drug residues in the device will hinder all following inhalations.
- Whether disposable inhalers can make a therapy cost-effective or not does not depend on the price of the administration device alone.

This box summarises key points contained in the article.

In addition to ancient vapour baths, three different groups of aerosol delivery devices are historically available: classic jet and ultrasonic nebulisers, metered dose inhalers (MDIs) and DPIs. Nebulisers making use of (vibrating) mesh technology or ultrasonic nebulisers, metered dose inhalers (MDIs) and DPIs. Nebulisers making use of (vibrating) mesh technology have been added to the list [20-23], and they all exist in a variety of different designs. Principles of which as yet only one example can be given are, for instance, the Boehringer Respimat [24] and the Alexza Staccato [25] and a few more innovative principles are in an early stage of development. The Respimat creates aerosols by impingement of two liquid jets, whereas the Staccato inhaler vaporises drug from a chemically heated pad that condensates into a suitable aerosol during inhalation. Whether all these new principles can be used as disposable devices or not depends on how cheap they can be produced and whether they can be operated stand alone (i.e., without external energy source). In addition to the development of new pulmonary delivery systems, different trends can be observed in pulmonary therapies and they may indicate where opportunities and needs for the application of disposable devices exist. In this respect, disposable can have different meanings. It can refer to ‘single-use’ for a single dose, or to ‘disposable’ after a short period of use (e.g., 15 days, as for dry powder insulin, Afrezza). Also, disposable nebulisers have a limited lifespan of, for instance, 15 days or 15 treatments (e.g., Pari LC D) but when used to treat patients with infectious diseases in hospitals, even reusable nebulisers are best discarded after completing the therapy. In that sense they should be considered as ‘single-patient’ devices. Single doses may comprise multiple powder quantities to be inhaled, as for instance dry powder tobramycin with the Podhaler.
(a single dose is divided over four capsules), but the Podhaler according to the definitions given is not a single-use, but a disposable inhaler as it lasts 1 week before it must be replaced.

2.1 Asthma and COPD
The economically most relevant trend of the past two decades is indisputably the market introduction of a large number of generic devices for inhaled corticosteroids (ICS) and \( \beta_{2} \)-agonists for the treatment of asthma and COPD [26]. In many countries, this development and the pressure on healthcare budgets have resulted in a significant switch from branded to generic medication and the process will be continued for combination products with two or more drugs. The chronic nature of these diseases mostly requires a lifetime treatment with a high frequency of drug administration. Multiple doses have to be inhaled daily and reusable multidose, multiple unit-dose (blister) or refillable single-dose (capsule) inhalers seem in general most appropriate for this application. Nevertheless, there may be situations and circumstances when disposable bronchodilator inhalers are more preferable. In many European countries, general practitioners have a salbutamol MDI with valved holding chamber (VHC) as relief medication for patients with acute bronchoconstriction. The VHC is washed, but not always disinfected before it is used again. It would reduce the risk of cross-infection and safe time when a disposable spacer could be used, and it has been shown that a simple disposable paper cup can be as effective as a reusable spacer for the first-aid management of asthma [27]. Alternatively, a single-use DPI could be used. It has been concluded from a literature analysis that DPIs function in patients with acute asthma and COPD equally well as established therapies with other inhaler devices [28,29]. Also, emergency departments of hospitals might benefit from single-use bronchodilator inhalers.

2.2 Bronchial challenge testing
Related to asthma and COPD are the bronchial challenge tests. In such tests, a bronchoconstrictor is administered to the airways to quantify airway hyperresponsiveness. Most frequently, methacholine is administered that acts directly on muscarinic receptors of smooth muscle cells, but also indirect stimuli like adenosine, mannitol and hypertonic saline are used. Only mannitol is currently commercially available as inhalation powder (Aridol, Pharmaxis Ltd.) and the administration is with the reusable ISF capsule inhaler [30]. Methacholine, adenosine and hypertonic saline are inhaled as wet aerosol and for adenosine different concentrations of AMP are prepared, as AMP has an ~50 times higher aqueous solubility than adenosine. AMP is often administered according to the dosing protocols for methacholine (e.g., the 2-min tidal breathing test) and the total test comprises nine different concentrations varying from 1.25 to 320 mg/mL. The time-consuming procedure is not only a burden for the test person, but also for the lung function analyst and the pharmacy department of the hospital, because the solutions are not stable and have to be prepared the day before the test is scheduled. Moreover, the test suffers from various inaccuracies and uncertainties [31] and it has recently been reported that the nebuliser test can successfully be replaced by a dry powder test using adenosine instead of AMP [32]. The dry powder test is well tolerated and much faster, the powder formulations have a much higher stability and the intention of this development is to use disposable DPIs and to develop similar formulations for methacholine in the same inhaler as well. Also, for metacholine, a dry powder alternative has already been tested successfully [33].

2.3 High-dose pulmonary antibiotics
Another noticeable trend is the replacement of classic jet and ultrasonic nebulisers for high-dose antibiotic administration to CF patients by alternative delivery devices. Classic jet nebulisers are not very efficient. They suffer from high residues in the nebuliser cup, aerosol losses to the environment during moments of exhalation and low deposition fractions in the respiratory tract [4]. Besides, nebulisation procedures are laborious and time-consuming and particularly when different drugs have to be inhaled they may cost the patient up to several hours in total per day. This is not only a heavy burden for the patient, it also results in incorrect inhalation technique (patients combine drugs with each other as well as inhalation with other activities), poor compliance with cleaning and disinfection procedures and poor adherence to the therapy. Incorrect cleaning of nebulisers is one of the reasons for incorrect performance [34] and this makes the therapy ineffective and the number of exacerbations and hospitalisations unnecessarily high. Alternatives focus on increasing the efficacy of drug delivery, shortening the administration time and reducing the cleaning procedures, and the approaches to achieve these goals seem to diverge into two different directions. On the one hand, (vibrating) mesh nebulisers have been introduced. They have reduced nebulisation times and examples are the e-Flow rapid (Pari), I-neb (Philips Respironics) and MicroAir NE-U22 (Omron) [20,23,35]. These modern liquid inhalers may need smaller volumes to be aerosolised and offer the possibility of patient monitoring or breathing pattern adaptive aerosol delivery [22,23]. They are complex however, and although they may have some exchangeable parts to minimise the risk of bacterial resistance development, they are too expensive to be entirely disposable. Therefore, they do not bring relief to the patient in respect of cleaning. On the other hand, some high-dose antibiotic DPIs have become available. Novartis launched tobramycin dry powder (TOBI), a PulmoShere formulation and almost in the same period Foster Laboratories presented micronised colistimethate sodium (Colobreathe) [36,37]. Both drugs are delivered with basically the same reusable capsule based DPI previously known as the Turbospin (PH&T). Also, dry powder inhalation shortens the administration time, although for the Podhaler with dry powder tobramycin the time reduction is limited as the total inhalation manoeuvre includes four capsules to be emptied in at least two inhalations each. It has been reported that this takes the patient 4 – 6 min [38]. The main reduction in
time is achieved by omitting the cleaning procedures. Wiping the mouthpiece with a dry cloth after getting the full dose is considered sufficient. This may not be good enough, however, because PulmoSphere tobramycin is a hygroscopic powder formulation, and this is a compelling argument for making the DPIs for antibiotic delivery in CF therapy single use [39].

Many other infectious diseases are treated with high-dose antibiotics, and a disease of particular interest having a high priority for improvement of the therapy is tuberculosis (TB). Currently, TB is treated with a long course of antibiotics, depending on the type of the disease, given by the oral or parenteral route. Pulmonary administration could be a good alternative for this disease too, but patient cross-infection is a risk when reusable delivery systems are used. Hospitalised patients on inhaled medication should therefore be treated with single-patient administration devices. More preferably, single-use devices are applied to completely eliminate the risk of interchanging devices between patients. TB is a worldwide health risk due to the rapid increase in the emergence of multidrug and extensively drug-resistant strains (MDR and XDR) with rates as high as 35% in some parts of the world [40]. New drugs or delivery systems are urgently required and inhalation could become a successful alternative to oral and parenteral administration [39,41,42]. The much higher local concentrations that are potentially achieved via the pulmonary route would result in a much better therapy with the first-line antibiotics, even in cases of MDR-TB. Also, second-line and new antibiotics can be much more effective when being inhaled, whereas synergistic effects from drug combinations may be more pronounced due to a much better control of the desired drug concentration ratio on the site of infection. Some antibiotic drugs tested or in development for administration as dry powder are, for instance, gentamicin [43,44], ciprofloxacin [45,46], moxifloxacin and ofloxacin [47] and capreomycin [48].

2.4 Pulmonary vaccination

The idea to consider the respiratory tract a suitable port of entry for vaccines is also relatively new. Yet, many reviews on pulmonary vaccine delivery have been written and they have given a good survey of the diseases of interest [49,50]. The respiratory tract is the main port of entry for airborne pathogens of major diseases such as the influenza virus that invade the body through mucosal tissue. The lungs contribute one quarter (~ 100 m²) to the total mucosal surface area of the human body [51], and the mucosal immune system contributes nearly 80% of healthy adult’s immunocytes. Therefore, the respiratory tract is highly sensitive to antigens [52] and pulmonary vaccination has the advantage that it provides protection directly at the port of entry for pathogens. When produced as a dry powder, the stability of vaccines can be considerably higher than in liquid formulations, as has been shown, for instance, for influenza subunit vaccine [53]. This is of particular interest for vaccination programmes in developing countries that mostly have a warm climate and often a deficient cold chain storage and transport. Besides, vaccination is a once-only administration for a longer period of time and even if booster doses are involved, they may be given several weeks up to several years later. Therefore, disposable DPIs seem most appropriate for the administration of vaccines.

2.5 Miscellaneous for local action

In addition to the treatment of local inflammation, (bacterial and viral) infections, bronchoconstriction and vaccination, several other therapies for local action may be most effective via pulmonary administration and safe or convenient with disposable inhalers. For instance, (liposomal) amphotericin B [54] for the treatment of fungal infections has already been tested as dry powder. Also particularly interesting for inhalation as a dry powder are chemotherapeutics in lung cancer [55,56], drugs preventing rejection after a lung transplantation, like cyclosporine A [57,58] or drugs for the treatment of pulmonary arterial hypertension [59].

2.6 Systemically acting drugs

In contrast to locally acting drugs, the systemic treatment of diseases via the lung may require a higher drug dose than oral or parenteral administration. For inhaled drugs, the fastest absorption is achieved in the most distal airways [60]. The alveolar tissue in the lungs provides a large surface area for absorption as there exists a minimal barrier between the drug deposited and dissolved in the epithelial lining fluid and the bloodstream. Additionally, metabolic activity in the lungs is very limited. Different mechanisms are hypothesised that enable to bring larger molecules up to several kDa into the systemic circulation, and this opens the way for the administration of a variety of existing as well as new biopharmaceuticals via the lungs [61-67]. The first commercially available pulmonary drug for systemic action was insulin (Exubera, Pfizer) [36], and although the product was unable to meet the high market expectations and therefore, rapidly withdrawn, a successor (Afrezza, MannKind Corp.) is expected to obtain approval by the FDA in 2014 [68]. An approval has already been obtained for loxapine inhalation powder for acute treatment of agitation in patients with bipolar disorder or schizophrenia (Adasuve, Alexza Pharmaceuticals) [69]. More examples will follow, and one of the first new therapeutic drugs to be expected is inhaled dry powder levodopa (Civitas Therapeutics) for patients with Parkinson’s disease [70].

3. Arguments and opportunities for disposable inhalers

As explained in the previous paragraphs, different therapies and treatment regimens may require different inhaler technologies. Many new applications may become safer, more flexible and/or convenient for the patient and hospital staff with single-use or single-patient inhalers, and the most important reasons for having a preference for single-use devices are summarised in Table 1 and they need no further explanation. Table 2 presents
The role of disposable inhalers in pulmonary drug delivery

Table 1. Arguments in favour of disposable inhaler devices.

<table>
<thead>
<tr>
<th>Argument</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>To eliminate the risk of cross-contamination of diseases in mass vaccination programmes</td>
<td>To protect patients from cross-contamination with drug-resistant strains</td>
</tr>
<tr>
<td>To eliminate the risk of performance failure due to improper cleaning, poor maintenance or damage of formulation or device after falling (for dry powder inhalers with many moveable parts) or incorrect reassembling (nebulisers)</td>
<td>To avoid performance failure in the formulation or delivery of the drug</td>
</tr>
<tr>
<td>To avoid bacterial resistance development and patient reinfection with drug resistant strains</td>
<td>To prevent the development of drug-resistant strains in the clinic</td>
</tr>
<tr>
<td>To avoid water uptake and particle liquefying of retained fractions of hygroscopic drug formulations</td>
<td>To prevent water uptake and particle liquefying of the formulation</td>
</tr>
<tr>
<td>To increase cost-effectiveness, particularly in once-only administrations (e.g., vaccination)</td>
<td>To reduce the cost of therapy</td>
</tr>
<tr>
<td>To simplify the instructions for use by eliminating the need to operate a dose measuring principle</td>
<td>To make therapy easier for patients</td>
</tr>
<tr>
<td>To avoid needing descant compartments in reusable multidose inhalers that protect the drug formulation against moisture absorption</td>
<td>To protect the drug formulation from moisture</td>
</tr>
<tr>
<td>For hygienic reasons (inhaler pollution; spreading of inhaler residues in pockets and handbags)</td>
<td>To maintain personal hygiene</td>
</tr>
<tr>
<td>To reduce the inhaler size that makes them more portable</td>
<td>To make them easier to carry</td>
</tr>
</tbody>
</table>

Table 2. Arguments against disposable inhaler devices.

<table>
<thead>
<tr>
<th>Argument</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>For chronic diseases requiring frequent drug administration on a daily basis, disposable inhalers are not cost-effective</td>
<td>A stock package of disposable DPIs for a longer period takes more room than a multidose DPI</td>
</tr>
<tr>
<td>Disposable inhalers produce more pharmaceutical waste and patients may need to collect their used devices for intake by a pharmacy department</td>
<td>To reduce the cost of waste management</td>
</tr>
<tr>
<td>Scarce resources and environmental pollution may put pressure on the acceptance of disposable products</td>
<td>To reduce environmental pollution</td>
</tr>
</tbody>
</table>

some arguments that could be raised against single-use devices, but whether all of these points are really to be considered as a drawback or not depends on the situation with which they are compared or in which they are judged. For instance, disposable products impose a heavy burden on waste management and acceptance of single-use inhalers may be low in societies in which an environmental-friendly lifestyle and the use of durable consumer goods are encouraged. Recycling of waste material is expensive because it requires that recyclable products are collected separately from general waste. Single-use inhalers that may contain residues of the drug should not be mixed with other plastic disposables and preferably be returned to a pharmacy. However, collection of used inhalers through pharmacies is relatively easy to organise and the volume of inhalers is small compared with the volume of other disposable products like packaging materials and PET bottles. The risk of environmental pollution with used inhalers can be minimised by providing new inhalers only upon return of the used ones. And if single-use DPIs are replacing instable solutions for nebulisation or injection solutions, other aspects must be taken into consideration for the total burden imposed on the environment too. Cooled storage and transport consume energy and require the use of isolation materials and nebuliser residues are normally not returned to the pharmacy but simply flushed down the drain. Not to mention that environmental and cost aspects have to be considered in relation to safety and efficacy of the therapy to decide whether the total balance is in favour or against disposable inhalers. Some potential (future) applications for which they can be used are listed in Table 5.

A great challenge exists in minimising the volume of a stock package of medication for a longer period of time, particularly for patients that are travelling. When the single-use inhaler is a credit card-like DPI, the difference in volume may be limited, or even be to the advantage of the single-use device compared with, for instance, a nebuliser with an equal number of vials with drug solution plus syringes with needles. Empty vials and used needles are similar to used DPIs pharmaceutical waste, but they require the use of a special sharps container that may not always be available. The cost-effectiveness also depends on the situation. For drugs that are administered as a daily routine and are not hygroscopic, as ICS and bronchodilator drugs in asthma and COPD therapy, the cost price per dose will be higher with single-use than with reusable multidose MDIs or DPIs. A higher cost price per dose does not necessarily make the therapy more expensive however, and for a good estimation of cost-effectiveness additional healthcare costs should be taken into consideration as well [71]. Hygroscopic drug formulations, poor compliance with the cleaning instructions and/or incorrect operation of a dose measuring principle may make the therapy inefficient and increase the frequency of exacerbations and hospitalisations. Also, the costs for cleaning and disinfection of reusable inhaler systems used in hospitals have to be taken into account. Recently, it has been shown to what extent the cost-effectiveness of DPIs may depend on the price discounts offered by the manufacturers [72].

4. Starting points for design and requirements of disposable inhalers

To disposable inhalers basically the same requirements and regulations apply as to multidose inhalers regarding clinical efficacy and safety. Of the four different groups of aerosol delivery devices, only MDIs and DPIs are approved and registered systems for delivery of well-defined drug doses in labelled numbers. In contrast, all nebulisers are empty delivery devices. This makes it easier to develop disposable nebulisers than disposable DPIs because of the approval needed for the latter. Only a few nebulisers are officially approved for delivery of a special product, like the Pari LC Plus jet nebuliser (with suitable compressor delivering a jet flow of 4–6 L/min) for tobramycin nebulisation solution (TOBI) [73], or the Respironics I-neb or Prodose mesh nebuliser for iloprost (in the USA) [23].

By their design, MDIs are less appropriate as disposable inhalers, particularly for high-dose drugs. It may technically not be impossible to scale MDI canisters down to the size or volume of a metering chamber for a single dose, but to our
knowledge, such devices have not been introduced to the market yet. The only reference to a single-dose MDI that can be found is a patent (74) that mentions a canister containing a formulation with enough drug for only one administration or that is provided by a mechanism to lock the canister in a position where it cannot be actuated for a second dose. Although MDIs are cheap multidose delivery systems because of their relatively simple design and low production costs compared with DPIs, this might change after scaling them down to single-use inhalers. For these reasons, only DPIs and nebulisers will be discussed as potential disposable devices. For the different types of nebulisers, mostly only the nebuliser cup of jet nebulisers is disposable. Also, single-patient vibrating mesh nebulisers exist (e.g., Aeroneb Solo, Aerogen), but they are used primarily for drug administration to ventilated patients that are not the target patient population for this review.

For jet nebuliser cups, the design of disposables may not be too different from reusables although well-established manufacturers like Pari and Trudell provide different performance data for their reusable en disposable nebuliser cups. Differences refer to delivered fine particle dose and the mass median aerodynamic diameter of the aerosol, and this will have an effect on the site of deposition and thus, the efficacy of the therapy. Disposable (mostly single-patient rather than single-use) nebulisers find widespread application in hospitals and they are nearly always operated with compressed air systems (wall air). They seem relatively safe regarding the risk of microbial contamination as for instance with CF pathogens when they are disposed after 24 h (75). However, careful testing and selecting is necessary as differences in cost-effectiveness may be considerable and cannot be predicted from the specifications provided by the manufacturers (17). It has also been shown in a comparative study with nebulised tobramycin that many disposable jet nebulisers fail to meet the technical specifications of the recommended Pari LC Plus nebuliser for the administration of this type of drug (76). These differences in performance between different disposables as well as compared with the approved or generally accepted type of nebuliser for a particular type of drug should raise concerns about the efficacy of the therapy. Additionally, the risk of incorrect adjustment of the prescribed jet pressure or flow from the compressed air system is higher for disposable compared with reusable nebuliser cups that are more frequently used with an appropriate portable compressor.

The approval needed for disposable DPIs eliminates a great deal of uncertainty about their performance, although delivered doses from passive DPIs may vary more strongly with the patient’s inhalation manoeuvre than those from nebulisers. Beyond doubt, the greatest challenge in design and development of disposable DPIs is to keep them small, simple, cheap and yet highly effective with a consistent and patient independent performance. Simplifying design follows partly from not needing a dose measuring system, a dose counter and/or a desiccant compartment. Simplifying also refers to the operational procedures that must exclude errors as much as possible. Several concepts reviewed previously have shown that the basic concept can be very simple indeed and comprise not more than two to four parts, including the container (e.g., blister or capsule) for the formulation (9). Additionally, the number of operational steps can be limited to only one or two before the drug can be inhaled. Simple injection moulding, filling and parts assembling techniques are furthermore prerequisites for keeping the production costs low. An example of a simple disposable design is shown in Figure 1 for the Twincer, which was originally developed for the administration of high-dose colistimethate sodium, but is currently redesigned for other high-dose drugs too (77). This concept comprises three simple plate-like parts that are stacked and clicked together. The drug is stored in a blister with a peelable lidding foil. The inhaler has no moving parts and the patient only has to remove the lidding foil by pulling before the drug can be inhaled. In spite of a simple design, such small disposable inhalers can be highly effective when designed properly as shown in Figure 2 for inhaled insulin (Exubera). Compared with the Exubera inhaler (Figure 3), the Twincer produces between 1.6 and 1.9 times higher mass fractions in the most relevant aerodynamic size fraction (1–3 µm) for systemic action at 60 L/min with the particle engineered insulin (Exubera) powder (Figure 2A). Moreover, as measured with laser diffraction technique and expressed as volume median diameter of the aerosol produced, the dispersion efficiency of the Twincer is nearly independent of the dose between 1 and 12 mg and the same at 2 and 4 kPa, corresponding with 35 and 55 L/min, respectively (Figure 2B). From this combined effect of a much better dispersion at a considerably lower flow rate, approximately twice the peripheral deposition may be expected from the Twincer compared with the Exubera inhaler, proving that small, simple and cheap inhalers can be highly effective indeed. A special challenge for disposable inhalers for antibiotics is to increase the dose while maintaining good dispersion efficiency and minimising the inhaler

### Table 3. Examples of disposable dry powder inhalers developed for specific applications.

<table>
<thead>
<tr>
<th>Inhaler</th>
<th>Developed by</th>
<th>Developed for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cricket</td>
<td>Mannkind Corp.</td>
<td>Single self-administration therapies</td>
</tr>
<tr>
<td>PuffHaler</td>
<td>Aktiv-Dry</td>
<td>Disposable dry powder dosing kit (for vaccines) operated with a reusable bulb and valve system (97)</td>
</tr>
<tr>
<td>Staccato</td>
<td>Alexza Pharmaceuticals</td>
<td>Marketed as Adasuve for loxepine (25)</td>
</tr>
<tr>
<td>Twincer</td>
<td>University of Groningen</td>
<td>Colistimethate sodium and other high-dose carrier free drugs (77)</td>
</tr>
</tbody>
</table>
Inhalation of antibiotics against TB may require doses up to a few hundred milligrams, and such large powder quantities need to be delivered in the lowest possible number of inhalations to obtain good compliance with the inhalation instructions and adherence to the therapy.

5. Starting points for design and development of drug formulations

Drug formulations for disposable inhalers are not necessarily different from formulations for reusable devices unless they are meant for different applications or therapeutic strategies. The advantage of dry powder formulations over drug solutions in respect of stability has already been mentioned. The hygroscopic nature of, for instance, aminoglycosides makes them highly adhesive and cohesive and this, in combination with a high compaction tendency, results in poor dispersion performance. They are also prone to adhere onto inhaler walls and build up huge inhaler deposits that after exposure to high relative humidity > 60 – 70% transfer into a viscous syrup. This is fatal for further inhalations from the same inhaler. These disadvantageous physicochemical properties for inhalation are the reason why they are particle engineered into formulations with excipients to improve their delivery to the respiratory tract as a dry powder. A well-known example is the PulmoSphere formulation for tobramycin (Novartis), which contains the phospholipid 1,2-distearoyl-sn-glycero-3-fosfocholine, calcium chloride and sulphuric acid as excipients. Processing is with an emulsion-based spray-drying process into ultralow density and sponge-like particles that indeed have improved dispersion performance and reduced retention compared with the pure (micronised or spray-dried) drug [78]. The process steps and excipients used increase the powder mass and volume to be inhaled however, and as a consequence a single dry powder tobramycin (TOBI) dose comprises four capsules with 45 mg of powder each of which only 28 mg (62%) is the active drug (as free base). Disappointingly, the incorporation of the amphipathic phospholipid does not decrease the water absorption of the formulation (Figure 4). The moisture isotherm is almost the same as that of pure spray-dried tobramycin base; the only beneficial effect obtained in this respect is a minor decrease in the rate of water uptake, but this does not help when the inhaler is exposed to the ambient air over a longer period of time. Therefore, a disposable DPI is to be preferred for the hygroscopic aminoglycosides.

To avoid inhalation of an excess of powder, the use of excipients in high-dose drugs has to be minimised, but this should not result in more complex and multistep particle engineering processes as they make the powder formulations expensive. To keep disposable DPIs cheap, the first choice preparation techniques are simple micronisation, precipitation, controlled (anti-solvent) crystallisation or spray-drying. Spray-drying mostly yields less stable amorphous powders with increased water sorption that has a negative effect on the stability of the formulation. However, for aminoglycosides like tobramycin the difference in moisture uptake with micronised powder is negligible whereas spray-dried tobramycin has better dispersion properties. Not using or minimising the amount of excipients makes dispersion and inhaler retention more dependent on the physicochemical properties of the drug itself. This places high demands on the inhaler design and performance [39,79].

6. Disposable inhaler development: state of the art

The most interesting and promising disposable inhaler concepts have been described already quite in detail before [9]. Although several new designs can since be found in the patent...
literature and on the internet, they will not be mentioned in this manuscript because there is no information available about their performance. Most of them are the products of consultants, industrial designers and plastic manufacturers, and the inhalers were developed with no other purpose than to make them available for the pharmaceutical industry without knowing for what drug formulation they will be used. Their primary task is to dispense a well-controlled amount of powder consistently to the lung. They are mostly design variations of existing DPI technology based on classic formulation types, such as adhesive mixtures. Many of them make use of capsules and basically all capsule inhalers (e.g., Aerolizer, Arcus, Breezhaler, Flowcaps, Spinmatic, Twister) can be developed as single-use devices. Pharmaceutical companies using these devices have to adjust their formulation to the performance of the inhaler, which often includes the incorporation of new excipients, up to substantial amounts, and the use of complex preparation techniques. Examples are, for instance, the PulmoSphere formulations for the antibiotics tobramycin (Novartis) and ciprofloxacin (Bayer HealthCare Pharmaceuticals) in the former Turbospin capsule based inhaler, now referred to as Podhaler for tobramycin. For this application, the inhaler lasts only 1 week.

When the objectives are to maximise lung deposition, minimise the use of excipients and avoid complex preparation processes, which for many highly dosed drug applications is desired, more powerful inhalers and/or new technologies are necessary. It has already been shown that high doses of antibiotics can effectively be dispersed without particle engineering with a disposable inhaler concept that is specifically designed for delivery of such problematic compounds [77]. For this development, the inhaler design has to be adapted to the

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**Figure 2.** (A) Comparison of the in vitro deposition from the Exubera inhaler and Twincer for particle engineered insulin (Exubera) at 60 l/min. (B) Volume median diameter of the delivered insulin aerosol particles from the Twincer showing its dose and flow rate-independent insulin dispersion.

Dose weights for the Exubera inhaler (marked with *) are for marketed 1 and 3 mg blisters. They contain 1.7 and 5.1 mg Exubera formulation respectively. Dose weights (2, 4 and 6) for the Twincer refer to mg Exubera formulation derived from 3 mg blisters corresponding with 1.18; 2.35 and 3.53 mg insulin respectively.
physicochemical properties of the spray-dried drug. New technologies can, for instance, also be found in the Alexza Staccato for delivery of loxapine (Adasuve) via drug evaporation and condensation [25] and the Afrezza Technosphere insulin (Mannkind Corp.), which makes use of self-assembling carrier particles [80]. Also, universities contribute to new inhaler technology and a solution for high-dose drug delivery with a classic inhaler is presented by the university of Sydney with their Orbital multibreath inhaler [81,82]. This principle can also be used in a disposable DPI concept. Some of the most interesting disposable DPIs either developed for general use or a specific drug or drug class are shown in Tables 3 and 4. Not all devices mentioned in these tables are exclusively disposable; some of them may also be developed as reusable inhaler. The tables exclude inhalers developed for nontherapeutic use (e.g., Aerolife Energy, QuantumDesigns) and the numerous examples in the patent literature or on websites that have not yet been described in scientific papers (e.g., DoseOne, Micro Engineering Solutions; MonoHaler, RPC Formatec GmbH). Also, various me-too devices for local markets are disregarded.

For disposable nebuliser cups, the situation is basically different from that for DPIs as they are designed as general administration devices for aqueous drug solutions, suspensions or specific (e.g., liposomal) formulations. When used in hospitals, they are preferred over reusable nebulisers because incorrect cleaning and disinfection bears the risk of cross-contamination of diseases. Moreover, performance of reusable nebulisers may change in time due to wear and improper handling such as unclogging the jet orifice with a needle-like object, whereas the actual operational time in hospitals of reusable nebulisers is often not recorded. Because disposable nebulisers exist in a great variety of different types, having different output rates and delivering different aerosols, it is not difficult to find the optimal model for a specific drug and/or target site. To increase the variety of aerosol properties even further, nebulisers can be operated with different jet pressures, but this flexibility is also one of the major disadvantages of wet nebulisation. Because the effects of the physicochemical properties of the drug solution and the jet flow on the size distribution in the aerosol are often not known, there may also be uncertainty about the site of deposition and thus the efficacy of the therapy. For this reason, it is recommended that new types of (disposable) nebuliser cups are always tested with the drug before they are used.

Figure 3. The difference in complexity and size between the Exubera inhaler and Twincer.
7. Conclusion

With the rapidly growing interest in the pulmonary route for the administration of both locally and systemically acting drugs, it is expected that the need for new and improved inhaler technology will rapidly grow. Many new applications may require inhaler specifications that cannot be met with classic inhaler technology and for several of these applications disposable inhaler versions may be preferred. Disposable inhalers can eliminate cross-contamination of diseases in hospitals and patient reinfection with drug-resistant bacteria. They may also be wanted for hygienic reasons and to assure good dispersion of hygroscopic powders. By design DPIs and jet nebuliser cups seem most suitable as disposables, but jet nebulisers should be tested with the drug formulation at the available jet pressure first before using them. New disposable DPIs should preferably not be designed for general use, but in conjunction with the drug formulation to obtain an optimal performance of the combination.

8. Expert opinion

It is almost inevitable that the need for new inhaler technology and/or strategy for many new drugs and therapies will grow and for some of the new applications there may be a preference for disposable devices. The reasons for this preference may be different (Table 1) and depend on the application (Table 5) and the list of arguments presented in both tables may not yet be complete. For instance, there is an increasing awareness of several advantages, but also of the limitations of the concept ‘one inhaler suits all’. Children with smaller body volumes and lower total lung capacities do not need the same dose and are not able to generate the same pressure drop and inhale the same volume of air as adults. This may have consequences for the delivered dose from the device on the one hand and (systemic) side effects from overdosing on the other hand. Recently, it was shown that many children tend to exhale through their inhaler [83]. This could be a reason to consider disposable inhalers as a better option for this patient group than reusable ones, at
Table 5. Some potential (future) applications for disposable dry powder inhalers.

<table>
<thead>
<tr>
<th>Local, single-use (single-dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In general: all hygroscopic drug formulations</td>
</tr>
<tr>
<td>Relief medication in acute asthma or acute bronchoconstriction</td>
</tr>
<tr>
<td>Vaccination</td>
</tr>
<tr>
<td>Rescue medication against terroristic attacks (e.g., anthrax)</td>
</tr>
<tr>
<td>Antibiotics against transmission of infectious diseases (e.g., tuberculosis)</td>
</tr>
<tr>
<td>Chemotherapeutics in lung cancer</td>
</tr>
<tr>
<td>Cyclosporin A in lung transplant patients</td>
</tr>
<tr>
<td>Local, single-patient</td>
</tr>
<tr>
<td>Pulmonary infections (hospitalised patients)</td>
</tr>
<tr>
<td>Systemic, single-use (single-dose)</td>
</tr>
<tr>
<td>Levodopa in Parkinson’s disease</td>
</tr>
<tr>
<td>Relief medication against pain, migraine, and so on.</td>
</tr>
<tr>
<td>Viagra against erectile dysfunction</td>
</tr>
<tr>
<td>Drugs against nausea</td>
</tr>
<tr>
<td>Nicotine during smoking cessation</td>
</tr>
<tr>
<td>Loxapine in acute agitation</td>
</tr>
</tbody>
</table>

least for drugs for which efficacy of the therapy is more important than cost aspects (e.g., in diabetes therapy). Similar considerations may give preference to disposable inhalers for elderly with severely restricted lung function. They are often wheezy and exhibit high breathing frequencies that increases the risk of exhalation through the device that for DPIs may affect further use. Another example is the treatment of patients with Parkinson’s disease. The use of levodopa is associated with levodopa-induced dyskinesias (LID), and insufficient self-awareness of this side effect may result in taking more doses than needed to treat the real ‘off’ periods [84-86]. This further increases the risk of LID and other side effects (sensory, autonomic and psychiatric disorders), which is the reason why Parkinson’s patients often receive limited numbers of doses at the time. Multi-dose or multiple-unit dose inhalers seem therefore not appropriate unless they make use of separately dispensable dose compartments (e.g., capsules or blisters). Disposable DPIs could be a good alternative for this patient group too also because of their ease of operation.

In a previous review, it was already mentioned that childhood vaccination will become one of the most important applications for disposable inhalers [9]. Also, protection or treatment programmes against threatening infections as, for instance, with H7N9 (bird flu) [87], Severe Acute Respiratory Syndrome (SARS) [88] or Middle East Respiratory Syndrome (MERS) viruses [89], immunisation against bio-terrorism agents (e.g., anthrax, plague, tularemia, botulism and smallpox) [90] or therapies against difficult to cure diseases like MDR and XDR TB [91] may in future be served best with disposable devices. Such applications often start or take place in developing countries with a warm climate where stable dry powders are preferred over wet formulations for reasons discussed in the introduction [92-94]. However, the disposable DPIs to be used have to fulfil many different demands. First of all, for many applications, the inhalers have to be simple, inexpensive and yet highly effective and reproducible. Many recipients in, for instance, vaccination programmes will be inhaler-naive and the providers may not always be well-trained. A simple design will therefore facilitate correct use, preferably almost by intuition. Childhood vaccination is often a once-only administration, and a high degree of confidence in correct delivery of the dose is needed as incorrect delivery may result in insufficient protection. But also for systemically acting drugs like insulin with a very narrow therapeutic window, inhaler performance should be robust and largely patient independent. Patient independence can be improved by limiting the range of attainable flow rates, and this may be obtained with a higher resistance to airflow. Central and deep lung deposition may become more patient independent with a higher fine particle fraction delivered at higher flow rates [79,95]. Multiple inhalations for a single dose should preferably be avoided, and this requires that the amount of powder to be inhaled is minimised. Also for the purpose of keeping the inhaler cheap, an excess of excipients and complex preparation techniques should be avoided. This has the consequence that the performance of the DPI becomes more dependent on the physicochemical properties of the drug product and this needs the opposite approach for development of the inhaler-formulation combination as currently applied by most pharmaceutical industries. The formulation should not be adapted to the performance of an existing inhaler, but the inhaler should be designed to meet the properties of the drug compound best [79]. Only in this way can formulations be kept simple and cheap.

Correct dose delivery in multidrug therapies, as against MDR and XDR TB, may also benefit from having all drugs needed in the same inhaler, as prescribing different inhalers for the same patient is one of the major causes of incorrect use [96]. A high degree of confidence in correct delivery of the dose may be obtained from signalling of good inhalation technique to the provider and the recipient of the vaccine. Signalling can also help to improve the inhalation technique. To avoid complicating the disposable inhaler design, the use of a reusable add-on device for the signalling is needed and even that of a cheap disposable exercise inhaler can be considered. The add-on device should be designed to avoid contamination with pathogens.

Finally, cost-effectiveness is an important issue to consider in an era where health budgets are under stress [9]. For vaccination purposes, cost-effectiveness can easily be assessed provided that the different systems compared with each other yield the same degree of protection. However, for chronic therapies it may be very difficult to predict whether disposable inhalers are cost-effective or not as this may not depend on the price of individual devices, but rather on the long-term costs of the therapy. Several
aspect are of influence, including the efficacy of the inhaler, the compliance with the instructions for use and the adherence to the therapy that all affect the frequency of exacerbation and hospitalisation. Besides, for hospitalised patients, the risk of cross-contamination of diseases and the time needed for the staff to clean and disinfect inhalers should also be taken into account. In this respect, disposable inhalers can be distinguished into single-use (single-dose) and single-patient inhalers and it may be worthwhile to investigate which concept suits a particular application best.

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Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.

10. A first review on disposable inhalers describing the most interesting and promising concepts and developments more in detail.

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Declaration of interest
AH de Boer and P Hagedoorn both receive royalties from Novolizer and Genuair sales and are currently involved in the development of the Twincer disposable dry powder inhaler platform.
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