Review article

Inhalation device requirements for patients' inhalation maneuvers

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ABSTRACT

Background: Inhaled drugs are the mainstay of treatment for lung diseases such as asthma and chronic obstructive pulmonary disease. However, failure to use inhalation devices correctly can lead to a poorly controlled status. A vast number of inhalation devices exist and each device has specific requirements to achieve optimum inhalation of the drug. Currently, there is no overview of inhalation requirements considering all devices. This article presents a review of the literature on different inhalation device requirements and incorporates the data into a new inhalation flow algorithm.

Methods: Data from literature on commercially available inhalation devices were evaluated and parameters, such as inhalation flow rate, flow acceleration, inhalation volume, and inspiration time assessed for the required inhalation maneuver specific to the device. All agreed upon data points were used to develop an inhalation flow algorithm.

Results: The literature analysis revealed availability of robust data for the required inhalation flow characteristics for most devices and thus for the development of an algorithm. For those devices for which these parameters are not published, the minimum required flow criteria were defined based on published data regarding individual aspects of aerosol quality.

Conclusions: This review provides an overview of inhalation devices available on the market regarding requirements for an acceptable inhalation maneuver and shows which goals should be achieved in terms of inhalation flows. The presented algorithm can be used to develop a new computer based measurement system which could help to test and train patients' individual inhalation maneuvers with their inhalation devices.

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1. Introduction

Inhalation is the preferred route of drug administration for patients with lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). The development and introduction of the pressurized metered dose inhaler (pMDI) in 1956 provided the first handy, reliable inhalation device [1,2]. In the following period, the device became a worldwide success [2]. The quality of pMDIs has continually improved over time, particularly since the ban on chlorofluorocarbons (CFCs) [2]. With the required changeover to alternative propellants, several products were fundamentally modified, which also led to changes in aerosol quality that were relevant for practice [1–6]. Key achievements since the switch from CFC to HFA (hydrofluoroalkane) are devices with slower exit velocities and warmer plumes [2,3,6]. A reduction in speed, combined with smaller particles for some products, led to significantly improved lung deposition of the active drug particles [1,2,4–6]. Next to pMDIs, dry powder inhalers (DPI) play a significant role in the treatment of diseases such as asthma and COPD. In 1987, the first multidose DPI device with budesonide, an inhaled glucocorticosteroid (ICS), was used [7]. Today, in addition to pMDIs, there are a number of devices available with medications in powder form.

The quality of inhalation devices is generally high and active drug delivery is reliable if the devices are used properly. The key factors for successful inhalation, however, involve the right particle size and a proper respiratory maneuver on the part of the patient [6,8]. Each inhalation device requires a specific preparation for reliable drug delivery. One of the most common sources of errors in the application of pMDIs is the lack of coordination between inhalation and the actuation of the inhaler [6]. With DPIs, inspiratory flow rates that are either too low or lack the necessary initial acceleration compromise treatment success [6]. While the handling of the inhaler, such as preparation (e.g. removing the protective cap and preparing the dose), positioning of the device (e.g. keeping it vertical) and follow-up (such as replacing the protective cap and storing it in a dry place) can be monitored by a therapist observing the inhalation process, there is currently no validated and easily available method in place for monitoring the quality of the complete inhalation maneuver with different devices.

In an editorial entitled “Dry Powder Inhalers and the Risk of Error”, Terzano formulated the following questions and requirements regarding the necessary inhalation energy in the application of breath-actuated DPIs: “The issue of flow independence makes it imperative to determine two parameters for all breath-actuated DPIs: Below which flow rate does the DPI performance fall dramatically? Above which flow rate does the DPI performance become fairly stable?” [9] Similarly, Laube et al. pointed out in their task force report that “no manufacturer has stated the minimum flow for their DPI, although it is clear that this information is needed.” [6].

An overview of such flow limits for all inhalation devices on the market is still lacking. However, these data are necessary to assess the quality of an individual inhalation maneuver. For the development of a new computer-assisted measurement system that can be used to measure and assess multiple aspects of the inhalation maneuver with original devices including inspiratory flow rate, inhalation time, acceleration rate, and inhalation volume, it was necessary to determine a measuring algorithm based on known and published data regarding flow value limits of inhaler requirements and inhalation quality.

2. Materials and methods

A literature search was conducted for publications released between 1980 and 2015 with the aim of determining all dependencies of inhaler performance on inhalation flow rate and inhalation maneuvers. The year 1980 was chosen to ensure that we included and discussed all relevant data on optimum inhalation flow rates for modern DPIs which were first launched in 1987. No years prior to 1980 were reviewed, as they could not include data on HFA-MDs. Search terms included “inspiratory flow”, “inhalation maneuver”, “inhalation technique”, “inhalation volume”, “flow acceleration”, “drug delivery”, “inhalation device”, and specific product names. Furthermore, parameters that are important for good inhalation results with commercially available inhalation devices, including pMDIs, DPIs, and breath-actuated inhalers (BAIs) were searched for including the following: minimum required inspiratory flow rates (bottom limit of the flow rate), optimum inspiratory flow rates, maximum inspiratory flow rates (upper limit of the inspiratory flow rates), flow acceleration, inspiration time, as well as inhaled volume after release or achievement of the minimum required inspiratory flow. The results of the search were complemented by literature cited in review articles. Publications were considered for review if they provided clear product specific information regarding effects of various flow parameters (e.g. flow rate) on clinical outcome and/or on aerosol quality criteria such as output, mass median aerodynamic diameter (MMAD), fine particle dose (FPD) and fine particle fraction (FPF). If publications did not meet these criteria they were excluded, no other exclusion criteria were used. Existing systematic reviews were included in this review. Next to full published articles and reviews in English, German text books and publications as well as editorials, instructions for use, poster abstracts, summary of product characteristics, the United States Pharmacopoeia, assessments of the European Medicines Agency (EMA) as well as other materials that were considered to be important to the topic were included in this review.

Data for inhalation flow rates and – if deemed necessary–other inhalation parameters are presented and discussed for individual inhalers. All agreed upon data points were then used to develop a new algorithm which could be used to measure and interpret quality of the inhalation maneuver with different inhalation devices.
3. Results

The review of the literature revealed obstacles in making clear distinctions between optimum (sufficient) inhalation flow rates and still acceptable (borderline) flow rates for each device. Minimum required inspiratory flow rates to deposit the medication dose in the airways are described for some inhalers. In some cases, however, these are too low for optimal therapeutic effects. Data regarding flow value limits of inhaler requirements and inhalation quality are described in detail for individual inhalers.

3.1. Pressurized metered dose inhalers (pMDIs)

As stated in most literature, patients should inhale slowly when using a pMDI [6,10–19]. However, for physical reasons, there must be a minimum inspiratory flow rate for pMDIs below which the flow rate should not drop. So far, there have been very few studies or publications addressing this topic. Von Hollen et al. showed that for inspiratory flow rates of 15 L/min, the oropharyngeal deposition values for all 3 of the pMDIs investigated in this study (QVAR® HFA, ProAir® HFA, Atrovent® HFA) were higher than for flow rates of 30 L/min [10]. Therefore, an optimum inspiratory flow rate through a pMDI should be greater than 15 L/min while the lower limit for an acceptable flow rate is 10 L/min.

With respect to the precise optimum inhalation flow rate for pMDIs, no conclusive information on “modern” HFA aerosols is reported in the literature. For inhalation of terbutaline with a CFC metered dose inhaler, Newman et al. determined in 1980 an optimum inhalation flow rate of 25 L/min [16]. While Laube et al. recommended a flow rate of approximately 30 L/min as ideal [6], the source on which they base their recommendation does not provide any exact flow rate data and only states that the inhalation flow rate for pMDIs should be as low as possible [17]. Elliott et al. also stated that pMDIs typically require an inspiratory flow rate of 30 L/min [18]. However, this advice may be considered as ‘historical’, since the development of HFA aerosols quality is not taken into account. Given the availability of new evidence, it may be time to revise the limits of the optimum flow rate of pMDIs. The Easi-Breathe®, a breath actuated inhaler (BAI) is already triggered at 20 L/min [6] and this trigger limit for drug delivery is also accepted by regulatory authorities. Based on this information, we defined a flow rate of 20 L/min as the lower limit for an optimum inhalation flow for the measurement algorithm for all pMDIs.

Although pMDIs are generally considered to be relatively similar in terms of optimal technique, there are differences in terms of consistency of FPF at different flow rates between various devices. Based on the data of Johal et al., in which one pMDI delivered constant FPF at 30 and 60 L/min and another one released a higher FPF at 60 L/min than at 30 L/min, it could be assumed that there are differences among various pMDIs in terms of minimum flow rates [14,15]. Since most devices on the market are generic and product specific data are available for only a few drugs, it is currently not possible to determine whether for some systems a higher minimum required inspiratory flow rate should be recommended. However, in order to achieve optimum therapy results somewhat higher flow rate values should therefore be targeted.

Prior to the changeover from CFCs to HFA the recommended maximum inspiratory flow rate for inhalation with pMDIs was around 60 L/min [11]. As with all device types, there is increased risk of impaction at the back of the throat with fast inhalation flow rates [20]. However, Farr et al. have shown that pMDIs may not be as dependent on keeping below 60 L/min as is often thought [12]. Lung deposition results for a salbutamol CFC-pMDI (Ventolin®) from a microprocessor-controlled device (SmartMist) at different release times and slow, moderate and rapid inspiratory flow rates (30, 90 and 270 L/min) showed better lung deposition results with inspiratory flow rates of 90 L/min than with 30 L/min [12]. Changes in aerosol characteristics due to the change in propellants complicate the interpretation of studies performed in the CFC era. Many older study results on deposition characteristics of CFC pMDIs and the resulting recommendations for use may no longer be helpful today. More recent data obtained with HFA pMDIs allow the conclusion that the upper limit for inspiratory flow rates is considerably higher than 90 L/min [13]. In their in vivo studies on QVAR®, Leach et al. demonstrated that flow rates up to around 137 L/min do not influence active drug deposition in the airways [13]. Taking into account the characteristics of HFA, we defined a maximum flow rate of 120 L/min as a useful upper limit for measured inspiratory flow rates for the measurement algorithm for all pMDIs (including BAIs). Little has been reported in the literature about the consequences of exceeding the upper limit. Therefore, exceeding the limit does not necessarily constitute a critical mistake. Nevertheless, training should be used to prevent the user from exceeding the limit.

3.2. Spacers/valved holding chambers for use with pMDIs

Similar to pMDIs alone, little is known or published about the minimum required inspiratory flow rates for pMDIs with spacer attachments.

Usmani et al. measured the effect of slow (mean (±SD): 30.8 ± 4.7 L/min) and fast (67.1 ± 16.7 L/min) inspiratory flow rates on lung deposition and clinical response (lung function) with monodisperse particles. The aerosol generation and delivery system in this study was comparable to that of an MDI with spacer with no flow dependence and no requirement for breath actuation or coordination. Fast inhalation increased total lung deposition for small (1.5 μm) particles but decreased total lung deposition of larger particles (3 and 6 μm). Oropharyngeal deposition increased for all particle sizes, but significantly greater for the larger particles [8]. Mitchell et al. measured the performance of different sized valved holding chambers (VHC) as a function of flow rate with an Andersen eight-stage impactor. The flow rate ranges they used (28.3 L/min, 45 L/min and 60 L/min) were likely to be achieved by users [21]. In a different study, von Hollen et al. measured the impact of two different flow rates on the aerosol quality of albuterol with different spacer devices using a Next Generation Impactor (NGI). The FPFs were similar with flow rates of 15 and 30 L/min. The MMAD was slightly smaller at 30 L/min compared with a flow rate of 15 L/min. The optimum flow rate for the application of pMDI with spacers is likely dependent on the combination of pMDI and spacer in use [22]. In general, user instructions for spacers recommend an inspiratory flow rate around 30 L/min and below [22–24]. A flow rate of less than 15–20 L/min, the minimum flow limit of pMDIs in general, is possible with spacers but there is certainly a minimum necessary flow rate (>0), especially when VHC are used. The valves have different resistances and a minimum effort is necessary to open and close the valves. During tidal breathing in young children the inspiratory flow rate is about 8–16 L/min. This could be too low for some VHC [25].

3.3. Breath actuated inhalers (BAIs)

With the Autohaler®, the spray is released when the device reaches an inspiratory flow rate of approximately 30 L/min [6,19]. At lower flow rates, the user cannot trip the lock-out mechanism for the dose delivery, which means that no drug is released at flow rates below 30 L/min. To actuate the Easi-Breathe®, a flow rate of 20 L/min is required [6,19]. These values were incorporated into the algorithm.
3.4. Turbohaler®

A large amount of data is available for the Turbohaler®. However, the literature refers to various products with different active drugs and preparations. For this reason, despite the copious amount of data, the exact evaluating of a specific Turbohaler® product is difficult.

In general, a strong flow dependency is described for the Turbohaler® [6,26–44]. For this device, lung deposition, mass output, FPF, FPD and MMAD are considered to be dependent on the inspiratory flow rates used (Table 1). The flow rate range of approximately 30 L/min to 60 L/min is considered a gray area for the Turbohaler®. On the one hand, at a flow rate of 30 L/min mass output and an effect are measured; on the other hand, the results regarding aerosol quality are not optimum at flow rates below 60 L/min [14,26,32,34–36,39,40]. Abdelrahim et al. determined the dose emission characterization of the Bricanyl® Turbohaler® (terbutaline) at 10, 20, 30, 40, 50 and 60 L/min [38]. While the MMAD only showed a moderate dependence on inspiratory flow rate when above 30 L/min, the mass output and FPF varied depending on the flow rate used (Fig. 1a–c). Although some data for the Turbohaler® show that a low flow rate can lead to clinical effects for the administration of beta agonists (terbutaline), it is recommended that the flow rate should not be below a minimum of 30 L/min [6]. This is due to the fact that clinical drug efficacy (measured in conjunction with the inspiratory flow rate) has so far only been determined with beta agonists. However, these show a clinical effect even if only the large airways are reached. For a good anti-inflammatory effect of ICS, though, a high FPF is of great importance. Therefore, the inhalation results are satisfactory only at rates of approximately 60 L/min and higher [6,42,43].

With the introduction of the preparation Oxis® Turbohaler®, a modified device (Flexhaler™) became commercially available whose characteristics are slightly different from devices using mono substances such as terbutaline (Bricanyl®, Aerodur®) or budesonide (Pulmicort®). For example, the device resistance of the Oxis® or Symbicort® Turbohaler® is around 10% lower than that of former Turbohaler® generations [33]. For the “new” Turbohaler® (used for formoterol monotherapy and budesonide/formoterol combination) the aerosol output and quality also exhibit flow dependence in the flow rate range between 30 and 60 L/min [33,40,41]. The manufacturer AstraZeneca describes this flow rate dependence in the instructions for use of the Pulmicort® Flexhaler™ (the Flexhaler™ is identical to the Oxis® and Symbicort® Turbohaler®) [41]. The instructions state that “in vitro testing has shown that the dose delivery for the Flexhaler™ is dependent on airflow through the device, as evidenced by a decrease in the FPD at a flow rate of 30 L/min to a value that is approximately 40–50% of that produced at 60 L/min. At a flow rate of 40 L/min, the FPD is around 70% compared to a FPD at 60 L/min.” [41] In a study by de Boer et al. different DPIs were tested in vitro as a function of the pressure drop (2, 4 and 6 kPa) across the inhaler and the effects on FPF analyzed. Again, it was confirmed that below the pressure drop of 4 kPa, which corresponds to a flow rate of 58.8 L/min, the FPF (particle <5 μm) with the Symbicort® Turbohaler® falls significantly [44].

Based on the data in the literature, the following values were incorporated into the algorithm: A flow rate of <30 L/min for the Turbohaler® was defined as insufficient while a flow rate range between 30 and < 60 L/min was defined as acceptable but capable of optimization. A flow rate of ≥60 L/min allows for optimum inhalation.

To define the acceleration of inspiratory flow, the data of Everard et al. and the values of the software algorithm of the Inhalation Manager were used [27,45]. Using a Malvern Mastersizer (laser particle sizer), Everard et al. found that “failure to attain a flow rate of 30 L/min before 150 mL of air had passed through a Turbohaler® resulted in an aerosol volume median diameter increase from less than 6.6 μm to greater than 45.3 μm” [45]. For the treatment to be successful, it is therefore important to inhale forcefully from the start, especially when using the Turbohaler®. A flow acceleration of at least 0.7 L/s² should be targeted [27]. Otherwise, the inhalation is assessed as insufficient.

3.5. Diskus®

The Diskus® (Accuhaler®) is a medium resistance [6] multidose powder inhaler with 60 individual doses in a rolled up blister strip. For each inhalation, only one blister is opened and emptied. There are sporadic indications that for the Diskus®, a flow rate higher than 30 L/min can yield better inhalation results [26]. Kamin et al. observed a very low mass output at flow rate values < 60 L/min (18 L/min and 30 L/min) compared to higher flow rates (60 and 90 L/min) [26]. However, other in vitro and in vivo studies have shown that at an inspiratory flow rate of 30 L/min, constant amounts of the active drug are delivered and that increasing the flow rate does not quantitatively or qualitatively improve the released dose [6,46,47]. This value is also indicated as the minimum required inspiratory flow rate in international recommendations [6]. The chosen minimum flow rate for the Diskus® in the algorithm was therefore maintained at 30 L/min.

3.6. Novolizer®

The Novolizer® is a DPI with medium device resistance [6] so that patients can achieve flow rates of 90 L/min through the device [20,48,49]. In the literature, various data are reported with respect to the minimum required inspiratory flow rates for the Novolizer®. The data vary from 35 L/min [50], to 40 L/min [51], up to a range of 35–50 L/min [49,52–54]. Exceeding this limit does not limit the delivery of the active drug. If the minimum flow rate of 35 L/min to 50 L/min is reached, the Novolizer® emits an optical and acoustic signal (feedback) to the patient [50]. As with many other DPIs, the active drug is removed from the device even with a respiratory flow rate below this acoustic signal threshold value. The patient should therefore be sure to inhale forcefully and quickly from the very beginning.

As a flow rate of 35 L/min is described in each literature reference, this value was incorporated into the algorithm as the minimum required inspiratory flow rate [49–54]. The optimum flow rate, however, starts at 50 L/min [49,52–54].

3.7. Genuair®

The Genuair®, a DPI with medium resistance [55], looks nearly identical to the Novolizer® device but has several modifications. The minimum flow rate that releases the trigger mechanism for the acoustic and optical signal to the patient is, depending on the publication, set at 45 L/min [56,57] or 40 L/min [58]. However, it has also been described that the active drug is already delivered at a flow rate of 35 L/min, resulting in a clinically effective FPD within the required specifications [57]. In another study it was shown that a full dose of the drug is released at a flow rate of >25 L/min and at a flow rate of >35 L/min, a constant FPF is delivered. Despite these results, Van der Palen recommended an optimum trigger flow rate for the Genuair® of 40 L/min [58]. Taking all data into account, we defined a value of 40 L/min as the minimum inspiratory flow rate for Genuair® and incorporated it into the algorithm.
<table>
<thead>
<tr>
<th>Device</th>
<th>System</th>
<th>Minimum required inspiratory flow rate values (in L/min)</th>
<th>Flow-resistance</th>
<th>Important aspects to consider</th>
<th>Recommended inhalation mode [6]</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMDI</td>
<td>pMDI</td>
<td>10</td>
<td>20</td>
<td>Much lower in comparison to DPI [55]</td>
<td>Slow exhalation as far as comfortable. Slow and deep inhalation (4–5 s) through the mouth until the lungs are filled with air. At the beginning of the slow inhalation the canister should be pressed to actuate the dose.</td>
</tr>
<tr>
<td>pMDI + spacer</td>
<td>pMDI + add on device</td>
<td>15</td>
<td>20</td>
<td>Low [55,88]</td>
<td>Coordination required. Coordination should occur in periods of seconds [6,89–92]</td>
</tr>
<tr>
<td>Autohaler®</td>
<td>Breath actuated inhaler</td>
<td>30</td>
<td>30</td>
<td>Lower in comparison to DPI [55]</td>
<td>The threshold value is attained at 30 L/min [6]</td>
</tr>
<tr>
<td>Easi-Breathe®</td>
<td>Breath actuated inhalers</td>
<td>20</td>
<td>20</td>
<td>Lower in comparison to DPI [55]</td>
<td>The threshold value is attained at 20 L/min [6]</td>
</tr>
<tr>
<td>Diskus®</td>
<td>DPI-blister</td>
<td>30</td>
<td>30</td>
<td>Medium [6]</td>
<td>Exhalation into the room to functional residual capacity before inhaling (no exhalation into the device). Forceful inhalation through the mouth from the very beginning.</td>
</tr>
<tr>
<td>Easyhaler®</td>
<td>DPI-multidose</td>
<td>30</td>
<td>30</td>
<td>High [6]</td>
<td></td>
</tr>
<tr>
<td>Aerolizer®</td>
<td>DPI-capule</td>
<td>40</td>
<td>40</td>
<td>Low [6]</td>
<td></td>
</tr>
<tr>
<td>Handihaler®</td>
<td>DPI-capule</td>
<td>20</td>
<td>30</td>
<td>High [6]</td>
<td></td>
</tr>
<tr>
<td>Brezzhaler®</td>
<td>DPI-capule</td>
<td>50</td>
<td>50</td>
<td>Low [55]</td>
<td></td>
</tr>
<tr>
<td>Elipta®</td>
<td>DPI-blister</td>
<td>30</td>
<td>30</td>
<td>Medium [55]</td>
<td></td>
</tr>
<tr>
<td>Spiromax®</td>
<td>DPI-multidose</td>
<td>30</td>
<td>30</td>
<td>Medium-high [55]</td>
<td>After exceeding a flow rate threshold of 35–50 L/min, an acoustic (“click”) success signal is emitted and the inhaler is reset to prepare the next dose. For this reason, the threshold has to be exceeded [52]. After exceeding a flow rate threshold of 40 L/min, an acoustic (“click”) signal is emitted to reset the inhaler to prepare the next dose. For this reason, the threshold has to be exceeded [58].</td>
</tr>
<tr>
<td>Novolizer®</td>
<td>DPI-multidose</td>
<td>35</td>
<td>50</td>
<td>Medium [6]</td>
<td></td>
</tr>
<tr>
<td>Genuair®</td>
<td>DPI-multidose</td>
<td>40</td>
<td>40</td>
<td>Medium [55]</td>
<td></td>
</tr>
<tr>
<td>NEXThaler®</td>
<td>DPI-multidose</td>
<td>35</td>
<td>35</td>
<td>Medium-high [55]</td>
<td>Breath actuated threshold, no drug delivery below this threshold [71]</td>
</tr>
</tbody>
</table>

DPI – dry powder inhaler; pMDI – pressurized metered dose inhaler.
Fig. 1. A) Bricanyl® Turbohaler® (terbutaline) flow dependence on MMAD, mean values at different inspiratory flow rates of 10 L/min to 60 L/min, B) Turbutaline (Bricanyl® Turbohaler®) output, mean values in % of nominal dose at different inspiratory flow rates of 10 L/min to 60 L/min, C) Terbutaline (Bricanyl® Turbohaler®) fine particle fraction (FPF), mean values in % of nominal dose at different inspiratory flow rates (10 L/min to 60 L/min) (modified according to [64]).

3.8. Easyhaler®

Different *in vitro* studies have shown that the minimum required inspiratory flow rate of the Easyhaler®, a DPI with high resistance [6], is 30 L/min [59–62]. Vidgren et al. studied the flow rate dependence of the dose constancy of a salbutamol Easyhaler® at flow rates of 20, 28, 40 and 60 L/min. They showed that it was possible to inhale a therapeutic dose even at a low inspiratory flow rate of 28 L/min, although the respirable fraction (defined as particles <6 μm and respirable dose as the proportion of the delivered particles) achieved with a flow rate of 28 L/min (31.5%) was clearly below the value reached at 60 L/min (45.2%) [59]. In comparison to the Turbohaler®, the Easyhaler® is less dependent on the flow rate and delivers a higher FPF even at low flow rates (30 L/min) [60]. Koskelä et al. demonstrated that a low inspiratory flow rate of 29 L/min, the Easyhaler® (salbutamol) produces comparable improvements in pulmonary function as a properly used pMDI with a spacer [61]. Based on these studies the minimum required inspiratory flow rate for the Easyhaler® was defined as 30 L/min and incorporated into the algorithm.

3.9. Aerolizer®

The Aerolizer® is a single-dose capsule DPI with a low resistance [55] in which the active drug is inserted into the device in a gelatin capsule. Prior to each use, a needle is used to pierce the capsule which allows the active drug to be released. Compared with blister or reservoir DPIs, for capsule-powder devices the dose is released later and for this reason, inhalation quality depends on the volume inhaled. In order to be sure to actually inhale the complete dose per capsule, patients should repeat the inhalation procedure with the same capsule [6].

Weuthen et al. used an Andersen Cascade Impactor (ACI) to investigate the particle size distribution and MMAD generated by the Foradil® P Aerolizer® at inspiratory flow rates of 28.3, 40, 60, and 80 L/min. Based on the results, a flow rate range between 40 and 60 L/min was reported to be optimum [32]. Regarding the FPF (in % of the delivered dose, particles <5.8 μm), the optimum flow rate of the Foradil® P® Aerolizer® was reached at 80 L/min [32]. In earlier studies, the Aerolizer® was tested *in vivo* in 16 children between the ages of 8 and 15 with exercise-induced asthma. The study compared prophylactic inhalation of 12 μg formoterol inhaled at flow rates of 60 and 120 L/min and the authors concluded that the highest possible inspiratory flow rate should be reached in order to achieve the maximum effect [63]. In a more recent study, however, the optimal inhaler performance was found at 65 L/min. At this rate the pharyngeal deposition is low and the release from the capsule and the FPF is high [64]. In contrast to these results, Meyer et al. found that within a flow rate range from 30 to 130 L/min changes in lung deposition are less than 10% [65].

Due to the amount of published data in the literature, the required minimum flow rate through the Aerolizer® was defined to be 40 L/min for the algorithm. The optimum peak inspiratory flow rate is 65 L/min.

3.10. Handihaler®

The delivered dose of the Handihaler®, a DPI with high resistance [20], was measured by Chodosh et al. in the flow rate range of 20–60 L/min [66]. The results of studies using the ACI showed a dose release at flow rates as low as 20 L/min. It was further shown that the FPD and FPF (defined as the mass fraction of particles with aerodynamic diameters up to 5.0 μm) were similar across the flow rate range from 28.3 to 60 L/min. However, if the flow rate was reduced from 28.3 to 20 L/min, the FPD decreased by 20% [66]. In a more recent study, Lindert et al. have shown that the Handihaler® performance was not affected by the flow rate when flow rates of 30 an 60 L/min were compared; only the standard deviations were higher using a flow rate of 30 L/min, suggesting that this value represents a threshold [67]. Based on the results it can be concluded that the minimum required inspiratory flow rate is 20 L/min. At a flow rate of 28.3 L/min and higher, however, significantly better drug delivery values are achieved. Therefore, a flow rate value of 20 L/min is acceptable but a higher flow rate on the order of approximately 30 L/min is targeted. These values were incorporated into the algorithm.

3.11. Breezhaler®

The Breezhaler® is another DPI for which the individual doses are in capsule form. The flow resistance is comparatively low [55,68–70]. In an *in vitro* study, Pavkov et al. reported on the flow rate dependency of the delivered dose. The dose delivery (indacaterol) was determined at flow rates of 30–100 L/min. The aerodynamic particle distribution was determined with a NCI. At inspiratory flow rates of 50–100 L/min, approximately 80% of the target dose was delivered and the fine particle mass remained consistent. At an inspiratory flow rate of 100 L/min, a greater mean dose could be delivered with a lower deviation [69]. Chapman et al. described the results of an *in vitro* study in which the characteristics of the delivered indacaterol dose from the Breezhaler® were investigated. The study was performed using an NCI with an air flow rate of 100 L/min. Inhalation profiles of seven patients were selected to be representative of a COPD population, including patients with moderate and severe stages of COPD. The study revealed that a flow rate of 100 L/min generated a high FPF (defined as fraction of 150 μg label claim and particles <5 μm in diameter) of 26.8% and a comparably good intrathoracic deposition of 31%. The
mean size of the drug particles was 3.2 μm [68].

Based on the literature, the minimum required respiratory flow rate for the Breezhaler® is 50 L/min, with a maximum flow rate of approximately 100 L/min. The data of Pavkov et al. suggest an optimum peak flow rate in the range of 90–100 L/min [69]. In this flow rate range the highest delivered dose and fine particle fraction are obtained.

3.12. NEXThaler®

The NEXThaler® is a DPI with medium/high resistance [55] (containing beclometasone and formoterol) and with a breath-actuated mechanism guaranteeing that the dose is released only when a threshold inspiratory flow rate of 35 L/min is achieved [71]. In vitro data have shown that the NEXThaler® DPI device was able to consistently release a high FPF for inhalation flows rates from 30 to 90 L/min [71].

For the algorithm, the minimum required inspiratory flow rate for the NEXThaler® was set at 35 L/min.

3.13. Ellipta®

Ellipta® is a device with medium resistance [55] containing the active drugs fluticasone furoate and vilanterol (fixed combination). According to Hamilton et al., the delivered dose from Ellipta® is consistent over a flow rate range of 43.5–130 L/min for both investigated active drugs. Recently published in vitro data show that the Ellipta® inhaler delivers doses close to the stated label claim at flow rates between 30 and 90 L/min [72].

Based on these data an exact lower limit for an acceptable inspiratory flow rate cannot be determined for the Ellipta®. Data exist only within a measured flow rate range and no exact data are available below 30 L/min. However, good inhalation can be achieved with a value of 30 L/min and above, and these values were therefore incorporated into the algorithm.


DuoResp® Spiromax® is a novel multi-dose DPI with medium/high resistance [55] containing the active drugs budesonide and formoterol. Dose-delivery studies were performed using low-, middle-, and high-strength DuoResp® Spiromax® and total emitted doses were measured at various flow rates (40–90 L/min). The results have recently been published and show that even though total emitted doses tended to increase with flow rate, the extent of change was limited, so that all doses were within 15% of the labelled quantity. The results of this study were essentially the same for all three strengths of DuoResp® Spiromax®. The authors concluded that a minimal inspiratory flow rate of ≥30 L/min is required for effective treatment but that a flow rate of 60 L/min is preferred [73]. For the algorithm, the minimum required inspiratory flow rate was set at 30 L/min.

3.15. Development of an algorithm

An overview of the required inspiratory flow rates for the use of different inhalation devices is shown in Fig. 2. The flow rate requirements have been defined and described by means of a traffic light system. According to this diagram, flow rate values that are too low and therefore insufficient for effective inhalation are displayed in red. Borderline results such as minimum required inspiratory flow rates that do not yield optimum effectiveness yet are displayed in yellow, and values with optimum mass output, lung deposition and effectiveness outcomes are displayed in green. By looking at data on normal inspiratory flow rates (tidal breathing in seated position: approximately 18 and 13 L/min for men and women, respectively [74]), it can be seen that pMDIs can be used within the range of tidal breathing. For DPIs additional effort is necessary to overcome the device specific resistance to reach the required flow
rate [6]. During exercise, e.g. at the end of an ergospirometry test, peak inspiratory flow rates of 300–400 L/min can be achieved depending on age and height. Additional flow resistances such as DPI devices decrease these values significantly.

Every breath-actuated DPI has a minimum threshold in terms of flow efficiency. If the inspiratory flow rate is too low (or the flow acceleration below a threshold), deagglomeration is insufficient and a reduced dose is delivered (see Fig. 3) with a high MMAD and low FPF [6,9,28].

The upper flow limit for DPIs is generally physiologically limited by higher resistances compared to MDIs. Moreover, when using DPIs, patients should generally use a higher inspiratory flow rate from the very beginning in order to deagglomerate the powder [6]. As with MDIs, the in vitro outcomes of very high peak inspiratory flow rates with DPIs have rarely been reported in the literature. For that reason, no clear upper flow limit could be defined for the algorithm. Pharmacopoeias specify an upper limit of 100 L/min for DPI testing [77] but higher flow rates are possible with low resistance DPIs [65,78]. For medium or high resistance DPIs, possible peak flow rates are restricted by physiological limits. Even though a threshold must exist above which the improvement of aerosol quality is compensated by an increased oropharyngeal impaction [20], no exact value is described in the literature. For example, Meyer et al. found that for the Aerolizer [8] device even for a large flow rate range from 30 to 130 L/min the changes in lung deposition are less than 10% [65]. Therefore, it can be assumed that good lung deposition results can be achieved with flow rates of 120 L/min and above not only for MDIs [13] but also DPIs. Because of this, the maximum optimum flow rate value for the algorithm was set at 120 L/min for DPIs as well as MDIs. Higher flow rates could be accepted but lower flow rates (<120 L/min) should be targeted.

For a good inhalation, further flow criteria such as inhalation time and volume are essential with all inhalation devices. Regarding the device specific requirements for pMDIs and DPIs a sufficient length of inhalation time is needed as the inhalation maneuver should last longer than the spray duration of pMDIs and should be long enough for DPIs to deliver the powder dispersion. The spray duration of pMDIs is between 150 and 360 ms [79]. For the Aerolizer [8] it was shown that at a flow rate of 60 L/min the powder residence time was 6.5 ms [80]. For other DPI devices no published data could be found. However, it is known that time of dose-emission is not comparable between different devices [81]. The minimum inspiratory volume is derived from the anatomical and physiological properties of adult patients [74]. A volume of 500 mL is prescribed for intubated and mechanically ventilated adult patients as it is defined as a value that guarantees drug delivery to the lower respiratory tract. An inspiratory volume of less than 500 mL and an inhalation time of less than 1 s were therefore defined as deficiency indicators in the evaluation of a measured inhalation maneuver [27]. With capsule DPIs, the user should inhale at least a volume of 500 mL after reaching the minimum required inspiratory flow rate [27]. Inhaling with blister and multidose DPIs, the flow acceleration is very important [6,27,45]. The lower limit of flow acceleration for use of DPIs (reservoir and blister) is 0.7 L/s [26,27]. Capsule Inhalers are an exception: the importance of acceleration for quality of the aerosol is less significant due to slower drug delivery [6].

Overall, the threshold values determined from the literature are the basis for the algorithm (Fig. 4) that can be used to reliably measure and interpret individual inhalation maneuvers for each of the considered inhalation devices.

For BAlS (Autohaler®, Easi-Breathe®) and the flow triggered DPI NEXThaler®, there is no necessity for monitoring the minimum required inspiratory flow rate as an acoustic signal is emitted when the trigger threshold is reached. However, it is still a good idea to monitor the inspiratory maneuver, since doing so allows other criteria to be determined such as inspiratory volume, flow acceleration and whether the inspiratory flow rates are in the recommended range.

Another issue that may affect the quality of the inhalation maneuver is the duration of breath holding after inhalation as this offers drug particles more time for to reach the airway wall by sedimentation or Brownian motion. This technique could be helpful in reducing the exhalation of very fine particles, but particle size, aerosol speed and duration and depth of inhalation also have an impact on drug deposition. It is questionable whether breath holding time is critical during the inhalation of powder particles, which must be inhaled with a fast and powerful airflow. Applying a breath hold period after inhalation does not appear to be an important constraint for DPI use by children [82]. There is no evidence from studies demonstrating the assumption that breath holding significantly influences the clinical effects of inhaled bronchodilators. This finding is supported by an analysis of the ADMIT (Aerosol Drug Management Improvement Team) consortium. The ADMIT members came to the result that “no studies have demonstrated improved bronchodilation or any long-term therapeutic consequences as a result” [83]. However, since it is possible that breath holding is beneficial when using inhaler devices, patients should be advised to hold their breath for at least 5 s until we know more.

4. Discussion

This review of the literature revealed distinct differences between inhalation devices regarding the optimum inhalation maneuver. Considering the multitude of different inhalation devices, patients should be aware of the optimum inhalation maneuver with their prescribed inhaler since incorrect inhaler usage is recognized as a major factor in worsening of disease outcomes. However, quite often inhalers are considered easy to use so that patients do not receive adequate training even though it has been estimated that up to 68% of patients do not use their pMDI or DPI correctly [84]. At the same time, up to 67% of nurses, doctors and respiratory therapists are also unable to adequately describe or perform critical steps of inhaler use [84]. These data point to an urgent need for better education as well as training and testing of patients’ inhalation maneuvers.

Currently available tools for testing inhalation quality usually measure single inhalation parameters such as inspiratory flow rates but do not reproduce the patient’s entire inhalation maneuver and/or are not available for all product groups. One such measuring device is the In-Check Dial®, a peak flow meter that uses various resistances imitating different inhalation devices to measure the inspiratory peak flow [85]. The In-Check Dial® can be used to test whether patients are able to produce the required flow rate for a certain inhaler and whether the flow rate is within an appropriate range. Since only the maximum flow rate can be determined, no information is provided on the amount of time required to reach this maximum flow rate after onset of inhalation – information that is very important for evaluating the inhalation process for DPIs. “Whistles” are mouthpiece adapters or dummy devices that use a whistle to provide information on whether the flow rate during inhalation was sufficient or not. In-Check Flo-Tone® is one example of this kind of adapter [86]. It was developed to facilitate the use of pMDIs for patients. Similar to the In-Check Dial® the In-Check Flo-Tone® does not provide further information on the inhalation maneuver. Another measuring device is Vitalograph’s Aerosol Inhalation Monitor (AIM™). AIM™ works with hygienic disposable DPI and pMDI simulators. The measurement system tests the inhalation maneuver by measuring and evaluating the actuation,
the duration of inhalation and the inspiratory flow rate, as well as the breath-hold time [87]. To illustrate the difference between good and poor inhalation technique, a lung pictogram is used to symbolize achievement of the goals. The AIM™ therefore offers a good method for monitoring the use of a pMDI. However, the measurement system does not offer reliable information for different DPIs. Only one DPI simulator is available for testing all DPIs. The AIM™ DPI simulator has only moderate resistance and is therefore unable to reproduce the range of DPIs available on the market. One exception to the above is the “Inhalation Manager”, a computer-assisted system that is able to reproduce and evaluate the quality of the entire inhalation process using original devices [26,27]. When evaluating the quality of individual inhalations, the measurement system draws on stored in vitro data and is able to estimate the aerosol quality released from the tested device depending on the inhalation maneuver for each inhalation. However, complex in vitro measurements (using an ACI) are necessary to determine flow threshold values if new inhalation devices need to be incorporated into the system. With the algorithm presented in this paper, a new computer based measurement system can be developed which does not rely on extensive measurements but instead is based on published data. It therefore allows rapid adaptation to new inhalers and product innovations, provided that data exist and are accurately described in the literature.

In conclusion, the gathered information in this review provides a comprehensive overview of inhalation systems available on the market regarding the requirements for an acceptable inhalation maneuver and shows which goals should be achieved in terms of inhalation flows (for an overview of all inhaler characteristics see Table 1). Although there are only a few possibilities in practice to measure patients’ inspiratory flow rates, prescribers should ensure that the patient can raise the required inspiratory flow rate to adequately operate the chosen inhalation device. The prescriber also has to be aware that the requirements for flow velocity, inhalation time and volumes should be reached. The performance of the patient (possibly depending on the severity of the disease) to achieve the required thresholds should be considered when selecting the inhaler. The presented algorithm can be used to develop a new computer based measurement system which could test all the above described flow parameters. Such a measuring tool could assist testing and training of patients’ individual inhalation maneuvers with their specific inhalation devices.

Author disclosure statement

During the last 3 years P. H. has received honoraria for attending advisory boards or giving lectures for the following companies: AstraZeneca, Astellas, Berlin-Chemie, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Forest companies, Mundipharma, Novartis, Nycomed and Teva. S.H. has received honoraria for lectures from Servier, GSK, AstraZeneca, Mundipharma and TEVA and consulting fees from Mundipharma and TEVA. K.S. has received honoraria for a consultant agreement with Boehringer Ingelheim and for presentations from TEVA, Mundipharma and Novartis. M.B. and R.M.C. are employees of Mundipharma GmbH, Germany. M.B. is responsible as Medical Affairs Manager Respiratory, R.M.C. is responsible as Medical Project Manager Respiratory.

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