New Inhaler Devices – The Good, the Bad and the Ugly

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Abstract
Drug delivery to the lungs is an effective way of targeting inhaled therapeutic aerosols and treating obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD). In the past 10 years, several new drugs for the management of asthma and COPD have been marketed and more are under development. These new therapeutic respiratory drugs have been furthered by innovations in all categories of pulmonary drug delivery systems to ensure optimal aerosolisation performance, consistency in efficacy and satisfactory patient adherence. In this review, we discuss the technological advances and innovations in recent inhaler devices and the evolving roles of pressurised metered-dose inhalers, dry powder inhalers and nebulisers, as well as their impact on patient adherence to treatment.

Introduction

The benefits of inhaled therapy for the treatment of obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD), have been recognised for many years. In comparison with oral or parenteral formulations, minute but therapeutic drug doses are delivered topically into the airways leading to local efficacy within the lungs [1–3]. Unwanted systemic effects are minimised, as the delivered drug acts with maximum pulmonary specificity combined with a rapid onset and duration of action [1–3]. Consequently, aerosol formulations of bronchodilators and corticosteroids are the mainstay of modern treatment for asthma and COPD [4, 5]. Aerosols are either solutions containing medications, suspensions of solid drug particles in a gas or dry powder solid particles, which can be generated from devices such as pressurised metered-dose inhalers (pMDIs), dry powder inhalers (DPIs) and nebulisers [1–3]. Inhalers differ in their efficiency of drug delivery to the lower respiratory tract depending on the form of the device, its internal resistance, formulation of medication, particle size, velocity of the produced aerosol plume and ease with which patients can use the device [1–3]. Efficiency of drug delivery may also be influenced by patients’ preference, which in turn affects patients’ adherence to treatment and, consequently, long-term control of the disease [1].

In recent years, several technical innovations have improved the performance of all existing categories of inhaler devices, and some new delivery systems have been developed that have high delivery efficiencies; notable among these are the so-called ‘intelligent inhalers’, which allow inhalation to be controlled and patients adherence to treatment to be monitored [6]. Compared with previous devices, the new aerosol drug delivery devices have
pulmonary deposition fractions of 40–50% of the nominal dose, which are significantly higher compared with the low levels of 10–15% of the nominal dose that were achieved in the past [7]. The increased efficiency of these newer aerosol drug delivery devices means that similar efficacy can be achieved with a lower nominal drug dose [6].

In this article, we review the principal innovative developments in pMDIs, DPIs and nebuliser designs that have recently been introduced or are in the pipeline. One may well wonder what the connection might be between the title of this article and the famous Sergio Leone western movie ‘The Good, the Bad and the Ugly’. Well, innovations in existing inhalers, as well as the development of new delivery systems over the last few decades, have led to significant improvements in inhalers efficiency (the good); however, delivery systems are not as harmless as both clinicians and patients may think (the bad), and, more importantly, they may be not as easy to use, thus reducing patients’ adherence and consequently treatment efficacy (the ugly). Thus, a thorough understanding of inhaler devices will enable us to limit the ‘bad’ and the potentially ‘ugly’ and allow the patients the opportunity to derive the ‘good’ from inhaler devices.

‘The Good’: Innovations in Pulmonary Drug Delivery Systems

Pressurised Metered-Dose Inhalers

The development of the first commercial pMDIs was carried out by Riker Laboratories in 1955 and marketed in 1956 as the first portable, multidose delivery system for bronchodilators. Since that time, the pMDI has become the most widely prescribed inhalation device for drug delivery to the respiratory tract to treat asthma and COPD [8]; between 2002 and 2008, about 48% of inhaled medications sold in Europe were delivered by pMDIs [8]. The relatively low costs (particularly on a cost-per-dose basis) of pMDIs and the wide variety of medications delivered by pMDIs has contributed to the popularity of this delivery system, particularly in developing countries, and will ensure continued use in developed countries, which are facing increased pressure to reduce health care costs [9]. The pMDI is a portable multidose device that consists of an aluminium canister, lodged in a plastic support, containing a pressurised suspension or solution of micronised drug particles dispersed in propellants. A surfactant (usually sorbitan trioleate or lecithin) is also added to the formulation to reduce particle agglomeration and responsible for the characteristic taste of specific inhaler brands. The key component of the pMDI is a metering valve, which delivers an accurately known volume of propellant containing the micronised drug at each valve actuation. The operation principle of the present pMDIs remains similar to the original 1950 push-and-breathe concept: pressing the bottom of the canister into the actuator seating causes decompression of the formulation within the metering valve, resulting in an explosive generation of heterodisperse aerosol droplets that consist of tiny drug particles contained within a shell of propellant. The latter evaporates with time and distance, which reduces the size of the particles that use a propellant under pressure to generate a metered dose of an aerosol through an atomisation nozzle.

Much of the innovation and improvement in pMDI technology has its roots in the significant corporate investment that began in the early 1990s as the industry transitioned to hydrofluoroalkane (HFA) propellant (table 1). Until then, pMDIs used chlorofluorocarbons (CFC) as propellants to deliver drugs; however, in accordance with the Montreal Protocol of 1987, CFC propellants began to be replaced by HFA propellants that do not have ozone-depleting properties [10], HFA-134a and HFA-227ca are propellants that contain no chlorine and their residence time in the stratosphere is shorter than that of CFCs, and therefore the global warming potential of HFA is substantially lower than that of CFCs. HFA-134a albuterol has been the first HFA-driven pMDI that has received approval in both Europe and the United States. This preparation consists of albuterol suspended in HFA-134a, oleic acid and ethanol; clinical trials have shown this preparation to be bioequivalent to CFC albuterol in both bronchodilator efficacy and side effects [11]. At the present, in most European countries, CFC-driven pMDIs have totally been replaced by HFA inhalers. The components of CFC-driven pMDIs (i.e. canister, metering valve, actuator and propellant) are retained in HFA-driven pMDIs, but their design has been refined. Two approaches were used in the reformulation of HFA-driven pMDIs. The first approach was to show equivalence with the CFC-driven pMDI, which helped regulatory approval, to deliver salbutamol and some corticosteroids. Some HFA formulations were matched with their CFC counterparts on a microgram for microgram basis; therefore, no dosage modification was needed when switching from a CFC to a HFA formulation. The second approach involved extensive changes, particularly for corticosteroid inhalers containing beclomethasone dipropionate, and resulted in

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solution aerosols with extra-fine particle size (mass median aerodynamic diameter $\sim 1.3 \mu m$) and high lung deposition $[12, 13]$; these extensive changes have led to a 2:1 dose equivalence ratio in favour of the beclomethasone extra-fine HFA-driven pMDI compared to CFC beclomethasone dipropionate $[12, 13]$. Patients on regular long-term treatment with a CFC pMDI could safely be switched to a HFA pMDI without any deterioration in pulmonary function, loss of disease control, increased frequency of hospital admissions or other adverse effects $[10]$. However, when physicians prescribe HFA formulations in place of CFC versions for the first time, they should inform their patients about differences between these products. Compared with CFC-driven pMDIs, many HFA-driven pMDIs have lower (25.5 vs. 95.4 mN) impact force and a higher (8 vs. $-29^\circ C$) temperature $[14]$. These properties partially overcome the ‘cold Freon effect’ $[14]$ that has caused some patients to stop inhaling their CFC resulting in inconsistent or non-existent dose delivery to the lungs. In addition, compared to CFC pMDIs, most HFA pMDIs have a smaller (from 0.58 to 0.2 mm) delivery orifice, which may result in a slower delivery of the aerosol plume, thus facilitating inhalation and producing less mouth irritation $[15]$. Another difference is that many HFA-driven pMDIs contain co-solvents, such as ethanol. This affects the taste and further increases the temperature and slows the aerosol velocity. pMDIs containing a fixed combination of beclomethasone dipropionate and the long-acting bronchodilator formoterol in a solution formulation with HFA-134a and ethanol with co-solvent $[12, 16, 17]$ have been developed (Modulite® technology; Chiesi, Parma, Italy). Interestingly, this formulation dispenses an aerosol characterised by extra-fine particles with a lower velocity and at a higher temperature than that obtained when CFCs are used as propellants. These three factors, i.e. smaller particle size, lower plume velocity and less temperature drop, may decrease upper airway impaction and increase airway deposition of particles, particularly to the smaller airways, compared with the same drug administered from a CFC-driven pMDI $[16–18]$.

A frequent complaint from pMDIs users is that it is difficult to determine when their pMDIs will be empty. In a study assessing patients’ satisfaction with current pMDIs, 52% of patients reported that they are extremely

| Table 1. pMDI technology changes |
|-------------------------------|-----------------|-----------------|
| **CFC-driven pMDIs**          | **HFA-driven pMDIs** | **Clinical implications** |
| Propellant | CFCs | HFA-134 and HFA-227 | HFAs have no ozone-depleting potential |
| Aerosol plume | High velocity Cold temperature ($-29^\circ C$) Spray emitted as a jet | Reduced velocity Warmer ($8^\circ C$) Rounder cloud configuration | Decreased oropharyngeal deposition Reduced chances of ‘cold Freon’ effect Difference in feel and taste |
| Particle size | MMAD: 3–8 μm | MMAD similar to CFCs with suspension pMDIs MMAD: 3–5 μm with solution pMDIs MMAD: 1.1–1.3 μm with extra-fine solution pMDIs | No major change Lower oropharyngeal deposition, enhanced deposition in the lung Enhanced deposition in peripheral airways |
| Metering chamber | Volume 50–100 μl | Smaller chamber | Less chances of leakage during storage Less chances of loss of prime (i.e. the first actuation after storage contains a reduced drug dose) |
| Actuator orifice | Orifice diameter $-0.5$ mm | Smaller ($-0.2$ mm) orifice | Greater chances of clogging during storage Reduced spray velocity which facilitates inhalation |
| Formulation | Creaming of suspension Variable puff-to-puff dosing Tail-off effect | Ethanol used as solvent Improved puff-to-puff dosing Only a few additional doses provided after a specified number of doses on label claim | No need to shake the aerosol before use of solution pMDIs More consistent clinical efficacy Less chances of misuse because spray content decreases substantially when additional actuations are used beyond the specified number of doses on the label claim |
| Priming | Needs priming before use | Variable priming requirements | Check priming instructions according to brand |
| Dose counter | Absent | Present on some devices | Underdosing or overdosing unlikely |
| Temperature dependence | Operates best in warm temperature | Less temperature dependence | Losing efficacy unlikely in cold weather |
| Cost | Inexpensive | Expensive | Could change cost-effectiveness |

MMAD = Mass median aerodynamic diameter. Adapted from $[3]$. 

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unsure and 10% are somewhat unsure of how much medication remains in their current rescue inhaler. With the addition of an integrated dose counter, 97% of patients reported that they could tell when to replace their inhalers [19]. This has been addressed by the incorporation of dose counters in the pMDI device. The importance of an integrated dose counter in the new pMDIs was emphasised in guidelines issued by the US Food and Drug Administration [20]. GlaxoSmithKline launched the first pMDI with built-in dose counter (Seretide Evohaler®) in 2004, and dose counters are now incorporated into several new pMDIs. Mechanical dose counters are designed to rely on an active event of firing, such as sound, temperature or pressure change, with their reliability being proven clinically [21]. The primary purpose of dose counters is to inform patients when their inhalers are empty, but dose counters and adherence monitoring devices attached to, or incorporated into, an inhaler could improve adherence to inhaler therapy, especially if the device is coupled to an electronic system reminding patients to take their treatment. Examples of these devices include the DOSER® (Meditrack, South Easton, Mass., USA), Smartinhaler® (Nexus6, Auckland, New Zealand) and the Propeller sensor (Propeller Health, Madison, Wis., USA). These electronic dose counters have relatively high costs and concerns remain regarding the reliability of battery life. Nonetheless, the incorporation of dose counters will become essential for pMDI development to improve disease management by preventing patients from using their inhalers beyond the recommended number of doses and thus receiving suboptimal treatment [22].

One of the biggest challenges associated with effective lung delivery using pMDIs is the difficulty some patients (particularly young children and elderly individuals) have to coordinate device actuation with inspiration [23]; this may lead to a significant reduction in drug deposition in the lungs, and, consequently, less therapeutic effects. Breath-actuated pMDIs are a development from the original press-and-breathe pMDIs to overcome the problem of poor coordination between pMDI actuation and inhalation [1]. Breath-actuated pMDIs contain a conventional pressurised canister and have a flow-triggered system driven by a spring, which releases the dose during inhalation, so that firing and inhaling are automatically coordinated [1]. Newman et al. [24] and Leach et al. [25] observed that drug deposition in the lung of patients using the Autohaler® (3M, St. Paul, Mich., USA), a breath-actuated pMDI, was essentially identical to drug deposition in the lung of patients with good coordination using a press-and-breathe pMDI of the same formulation, but was significantly higher than that for patients with a poor coordination using a press-and-breathe pMDI. Numerous studies have shown improved drug deposition and increased patient confidence that a dose was successfully delivered with the use of breath-actuated pMDI [24, 26, 27]. Using breath-actuated pMDIs, errors are less frequent than with standard pMDIs [28]. Overall, incorporating breath-actuated pMDIs into the patients’ regimen may improve overall disease control and reduce health care costs associated with asthma or COPD compared to conventional pMDIs [3] in spite of increased device costs and complexity. The Easi-Breathe® (Teva Pharmaceutical Industries Ltd., New York, N.Y., USA) is similar in function to the Autohaler, but automatically prepares the device for use when the patient opens the mouthpiece cover [26]. When the patient breathes in, the mechanism is triggered and a dose is automatically released into the airstream. The inhaler can be actuated at a very low airflow rate of approximately 20 l/min, which is readily achievable by most patients [26]. Not surprisingly, practice nurses found it easier to teach and patients learned its use easier than with conventional pMDIs [26]. Other breath-actuated pMDIs are the K-Haler® (Clinical Designs, Aldsworth, UK) and the MD Turbo® (Respirics, Raleigh, N.C., USA). With the breath-actuated K-Haler, the drug dose is actuated into a kinked plastic tube, which is straightened by a breath-operated lever, which releases the dose. The MD Turbo was developed as a device designed to fit a variety of commercially available pMDI; it includes an electronic dose counter that shows the patient how much medication is left in the inhaler, and actuation only occurs at a predetermined (30–60 l/min) inspiratory flow.

Further advances in pMDI technology are represented by devices which incorporate small microprocessors into inhalers themselves; these ‘intelligent’ inhalers allow inhalation to be controlled and adherence to be monitored [6]. These developments represent significant modifications to the pMDI as a patient interface and clearly require careful analysis of the patient benefits and justification of the additional final unit cost. The SmartMist® (Aradigm Corp., Hayward, Calif., USA) system [6] is a breath-actuated, battery-operated electronic device able to analyse an inspiratory flow profile and automatically actuate the pMDI at a predetermined point in the patient’s inhalation when predefined conditions of flow rate and inhaled volume coincide. The SmartMist inhaler effectively guarantees that the patient has good coordination of inhalation and activation of the aerosol jet from the pMDI, and that the inhaled volume and flow rate are...
both appropriate. A similar technology is used in the AERx Essence® device (Aradigm Corporation), in which a small volume of drug solution is forced through a nozzle array by a breath-actuated piston system [6]. Visual feedback is provided to the patient via a small screen. The device also includes a heater to reduce the droplet size [6].

Dry Powder Inhalers

DPIs are delivery devices through which a dry powder formulation of an active drug is delivered for local or systemic effects via the pulmonary route [1]. DPIs have a number of advantages over other methods of pulmonary drug delivery, for example, direct delivery of the drug into the deep lungs utilising the patient’s respiration, and they are increasingly being explored as devices for the delivery of systemic drugs. Successful delivery of drugs into the deep lungs depends on the interaction between powder formulations and device performance [29]. Dry powders for inhalation are formulated either as loose agglomerates of micronised drug particles with aerodynamic particle sizes <5 μm or as carrier-based interactive mixtures with micronised drug particles adherent to the surface of large lactose carriers [29]. The powder formulation is aerosolised through a DPI device, where the drug particles are separated from the carrier (from drug carrier mixtures) or de-agglomerates drug particles, and the dose is delivered into the patient’s deep lungs. In these systems, particle size and flow property, formulation, drug-carrier adhesion, respiratory flow rate and the design of DPI devices significantly affect performance [29]. The physical design of the DPI establishes its specific resistance to airflow (measured as the square root of the pressure drop across the device divided by the flow rate through the device), with current designs having specific resistance values ranging from about 0.02 to 0.2 cm H₂O/l/min [30]. To produce a fine powder aerosol with improved delivery to the lung, a low-resistance DPI requires an inspiratory flow of >90 l/min, a medium-resistance DPI requires 50–60 l/min, and a high-resistance DPI requires <50 l/min [30]. Of note, DPIs with a high resistance tend to produce greater lung deposition than those with a lower resistance [30], but the clinical significance of this is not known.

There is a wide range of DPI devices available on the market (table 2), which deliver either single or multiple doses, and are breath activated or power driven [1, 29]; however, the development of novel devices with new designs continues because the design of a device affects its performance [29]. The challenge is to combine suitable powder formulations with DPI designs that generate small particle aerosols [29].

Based on their design, DPI devices may currently be classified into three broad categories: the first generation,
single-dose DPIs; the second generation, multiple-dose DPIs, and the third generation DPIs, also known as ‘active’ or power-assisted DPIs. The first generation, such as for instance the Rotahaler® (GlaxoSmithKline) and the newer Handihaler® (Boehringer Ingelheim, Ingelheim, Germany) and Breezhaler® (Novartis Pharma, Basel, Switzerland), are breath-activated, single-dose devices in which a capsule of powder is perforated in the device with needles fixed to pressure buttons; with these inhalers, drug delivery is affected by particle size and de-agglomeration of drug carrier agglomerates or mixtures delivered by the patient’s inspiratory flow. Part of the newly developed DPIs or existing devices used for new powder formulations [31] are still low-resistance capsule-based DPIs. This has the disadvantage that powder properties need to be optimised with respect to both emptying of the capsule and good dispersion. Moreover, the low resistance of the capsule-based DPIs will lead to very high flow rates, which are at the cost of a more central deposition of the drug in the lung [29]. The second-generation DPIs fall into two main categories: multidose DPI devices, i.e. they measure the dose themselves from a powder reservoir, or multi-unit DPI devices, i.e. they dispense individual doses which are pre-metered into blisters, disks, dimples, tubes and strips by the manufacturer [32–34]. The Turbuhaler® (AstraZeneca, Södertälje, Sweden) and Diskus® (GlaxoSmithKline) are representatives of the former and latter categories, respectively, although many other different designs are presently in development. All these DPIs have some essential components incorporated in the device, such as a drug holder, air inlet, de-agglomeration compartment and a mouthpiece. The design of DPIs is developed in such a way that the device should induce sufficient turbulence and particle-particle collisions to detached drug particles from the carrier surface (interactive mixtures) or de-agglomerates particles from large agglomerates of drugs only. Drug delivery to the lungs with these inhalers ranges between 12 and 40% of the emitted dose [32–34]. The more recently developed second-generation DPIs which are commercially available are the NEXThaler® (Chiesi), Ellipta® (GlaxoSmithKline) and the Genuair® (Almirall S.A., Barcelona, Spain). The NEXThaler delivers the fixed dose combination of formoterol fumarate and beclomethasone dipropionate as extra-fine particles for asthma treatment while the Ellipta device has been developed to deliver the new combination of the inhaled corticosteroid fluticasone furoate combined with the new long-acting β-adrenergic bronchodilator vilanterol as a once-daily inhaled maintenance therapy for asthma and COPD. Both of these devices are multidose DPIs with a simple three-step operation procedure, which can take into account typical human behaviour [35]: open the cover, inhale from the mouthpiece and close the cover (fig. 1). The NEXThaler
is equipped with an innovative full-dose feedback system incorporating a novel breath-actuated mechanism guaranteeing that the dose is released only when a threshold inspiratory flow of 35 l/min is achieved. A dose protector covers the dose and prevents the dose from being inhaled until the mechanism is triggered by a flow rate that allows complete de-aggregation and delivery of the full dose [36]. Of note, the NEXThaler is the only DPI delivering extra-fine particles and this unique characteristic depends on specific physicochemical properties of the powder formulation, as well as on the innovative de-aggregation release system [36]. The Ellipta is a multi-unit DPI which includes a dose counter; a recent exploratory study has shown that several attributes of the Ellipta, such as ease of use and simplicity of operation, the visibility and ease of interpretation of the dose counter, the feel and fit of the inhalation mouthpiece, and design ergonomics, are viewed positively by asthma and COPD patients [37]. Noticeably, the Ellipta was preferred to other inhalers by interview participants with asthma and COPD [37]. The Genuair (fig. 2) is a novel multidose DPI designed to deliver the long-acting anti-muscarinic bronchodilator aclidinium bromide from a non-removable cartridge [38]. The inhaler design includes visual and acoustic feedback to reassure patients that they have taken their medication correctly, a dose indicator and a lockout mechanism to prevent the use of an empty inhaler. The inhaler has medium airflow resistance and uses an optimised dispersion system to ensure effective de-agglomeration of the inhalation powder [38]. In vitro studies have demonstrated that the inhaler delivers a reproducible aerodynamic aerosol quality and is reliable under various thermal and mechanical stress conditions [38]. Further studies in vitro have demonstrated that the total emitted dose and fine particle dose are both consistent over a range of inhalation flows from 45 to 95 l/min, as well as being independent of inhalation volume (2 vs. 4 litres) and storage conditions [38]. In healthy subjects, delivery of 200 μg of aclidinium bromide via the inhaler achieved high lung deposition (approximately 30% of the metered dose) [39]. The high lung deposition observed in this study is consistent with the high fine particle dose generated from the inhaler in vitro [38]. A further study has shown that patients with moderate or severe COPD can generate sufficient inspiratory airflow through the inhaler to reliably inhale the full dose and reset the inhaler [40]. The third and newer generation DPIs are ‘active’, power-assisted devices, which incorporate battery-driven impellers and vibrating piezo-electric crystals (e.g. MicroDose®, MicroDose Therapeutx, Monmouth Junction, N.J., USA), to disperse drug from the formulation, thus reducing the need for the patient to generate a high inspiratory flow rate, an advantage particularly for patients with impaired lung function [33, 41]. Due to the presence of an energy source, active DPI devices enable respiratory force-independent dosing precision and reproducible aerosol production. In vitro studies have shown that active DPIs are able to produce aerosols characterised by fine particle fraction values in the range of 50–70% [41]. These devices are obviously more sophisticated than passive DPIs, and they are likely to be relatively expensive devices for asthma and COPD therapy, but could play a future role in the delivery of other drugs, such as peptides or proteins. The development of novel electronic DPIs, such as the MicroDose device, has shown that features such as dose delivery confirmation, adherence monitoring and dosing reminders can be incorporated into portable inhalers at relatively low cost [6].

**Nebulisers**

Various types of nebulisers are available on the market, and several studies have indicated that performance varies between manufacturers and also between nebulisers from the same manufacturers [42–44]. Jet and ultrasonic nebulisers have recently been joined by a third type using a vibrating membrane or mesh [42–44]. The jet (or pneumatic) nebulisers (e.g. LC Sprint®, PARI GmbH, Starnberg, Germany) remain the most commonly used nebulisers in clinical practice; they generate aerosol particles as a result of the impact between a liquid and a jet of high velocity gas (usually air or oxygen) in the nebuliser chamber. A 6–8 l/min flow and a fill volume of 4–5
ml are generally recommended, unless some nebulisers are specifically designed for a different flow and a smaller or larger fill volume [45]. With jet nebulisers, treatment times are generally long, the air compressors are heavy and noisy, and mechanical shear forces can affect certain medications. The longer nebulisation time with a greater fill volume can be reduced by increasing the flow used to power the nebuliser; however, increasing the flow decreases the droplet size produced by the nebuliser. Dead volume is the volume that is trapped inside the nebuliser and typically it is 0.5–1 ml. Because of the evaporative loss within the nebuliser, the solution becomes increasingly concentrated and cools during nebulisation.

Ultrasonic nebulisers (e.g. PolyGreen KN-9210; PolyGreen, Stahnsdorf, Germany) use a rapidly (>1 MHz) vibrating piezo-electric crystal to produce aerosol particles [42–44]. Ultrasonic vibrations from the crystal are transmitted to the surface of the drug solution where standing waves are formed. Droplets break free from the crest of these waves and are released as aerosol. The size of droplets produced by the ultrasonic nebuliser is related to the frequency of oscillation [42–44]. Although ultrasonic nebulisers operate silently, and can nebulise solutions more quickly than jet nebulisers, they are not suitable for suspensions and their piezo-electric crystal can heat the liquid drug in the reservoir, which renders it inappropriate for thermal-labile medications [3].

Vibrating mesh nebulisers are the newest technologies which overcome the disadvantages of both jet and ultrasonic nebulisers [46–48]. These new-generation nebulisers are either active or passive systems. In active devices (e.g. eFlow®, PARI GmbH), the aperture plate vibrates at a high frequency and draws the solution through the apertures in the plate. In passively vibrating mesh devices (e.g. MicroAir®, Omron Healthcare, Hoofddorp, The Netherlands), the mesh is attached to a transducer horn and vibrations of the piezo-electric crystal that are transmitted via the transducer horn force the solution through the mesh to create an aerosol. The PARI eFlow is designed to be used with either a very low residual volume to reduce drug waste or with a relatively large residual volume, so that it can be used instead of conventional jet nebulisers with the same fill volume [48]. Vibrating mesh nebulisers have a number of advantages over other nebuliser systems: they have greater efficiency, precision and consistency of drug delivery, are quiet and generally portable [46, 47]. However, they are also significantly more expensive than other types of nebuliser and require a significant amount of maintenance and cleaning after each use to prevent the build-up of deposit and blockage of the apertures, especially when suspensions are aerosolised, and to prevent colonisation by pathogens [46].

The principle of all the above-mentioned nebuliser types is that aerosol is generated continuously throughout the patient’s entire respiratory cycle (fig. 3). Thus, a large proportion of medication is lost during exhalation, resulting in inefficient aerosol drug delivery and variable dosing. Significant enhancements in drug delivery by nebulisers are possible by coordinating nebulisation with inspiration, i.e. the nebuliser is turned off during expiration (‘breath-actuated’ nebulisers; fig. 3) or utilising the patient’s inspiratory flow through the nebuliser to increase drug delivery (‘breath-enhanced’ nebulisers; fig. 3) [42, 43]. Both types of nebulisers are modifications of the ‘conventional’ jet nebulisers specifically designed to improve their efficiency by increasing the amount of aerosol delivered to the patient with less wastage of aerosol during exhalation [42, 43]. The breath-enhanced jet nebuliser (e.g. LC® Plus; PARI GmbH) uses two one-way valves to prevent the loss of aerosol to the environment. When the patient inhales, the inspiratory valve opens and aerosol vents through the nebuliser; exhaled aerosol passes through an expiratory valve in the mouthpiece. Breath-actuated jet nebuliser are designed to increase aerosol delivery to the patient by means of a breath-actuated valve (e.g. AeroEclipse®; Monaghan Medical Corporation, Plattsburgh, N.Y., USA) that triggers aerosol generation only during inspiration. Both the breath-enhanced and breath-actuated nebulisers increase the amount of inspired aerosol with shorter nebulisation time than ‘conventional’ jet nebulisers [42]. More recently, much greater control of nebulised aerosol delivery has been afforded by the coupling of software control with nebulisers [49–51]. These new-generation, ‘adaptive aerosol delivery’ nebulisers monitor the patient’s breathing pattern and continuously adjust the delivery of nebulised medication accordingly, thus leading to accurate high-dose pulmonary drug deposition in a much shorter time. By monitoring pressure changes relative to flow over the first three breaths, these delivery systems establish the shape of the breathing pattern and then use this to provide a timed pulse of aerosol during the first 50% of each tidal inspiration. Monitoring of the breathing pattern continues throughout the delivery period and any change in the breathing pattern is taken into account during the remainder of the delivery period. Furthermore, if no inhalation is registered, the system will cease delivery until the patient recommences breathing on the system [49–51]. Since the pulsed dose is only provided in the first 50% of each breath, and the software can calculate the amount of
drug given per pulse, the precise dose of drug can be delivered before the system stops [49–51]. The I-neb® (Philips Respironics Healthcare, Chichester, UK) and the Pro-dose® (Profile Therapeutics, Bognor Regis, UK) are examples of commercially available adaptive aerosol delivery systems approved in the US for delivery of inhaled prostacyclin to patients with pulmonary arterial hypertension and in Europe as multipurpose nebulisers. Both of these nebulisers use an adaptive aerosol delivery disk containing a microchip and antenna to control drug delivery. The I-neb is a vibrating mesh nebuliser, whereas the Prodose is powered by a compressor. In addition to delivering a precise drug dose, other useful features of the I-neb are the provision of feedback to the patient on dose completion along with details on each treatment. These data can be transmitted via a modem to a remote location, which enables continuing assessment of adherence of the patient to the drug regimen [3].

The AKITA® system (Vectura, Chippenham, UK) contains a SmartCard electronic control unit with an air compressor, which is coupled to either jet or vibrating mesh nebulisers [52]. The SmartCard software operates the air compressor unit to regulate the patient’s inhalation such that the AKITA system can accurately control

**Fig. 3.** Differences in the jet nebuliser design and aerosol output are indicated by the shaded area. 

a Constant-output pneumatic jet nebulizer.  

b Breath-enhanced jet nebuliser.  

c Breath-actuated jet nebuliser.
dose delivery and target nebulised aerosol to specific regions of the lungs. A vibrating mesh nebuliser using the AKITA system deposits 70% of the nebuliser fill in the lungs of patients with α1-antitrypsin deficiency [53]. Two different nebulisers controlled by AKITA were shown to increase total and peripheral lung deposition of an α1-protease inhibitor in patients with COPD compared to two other nebulisers used with spontaneous breathing [54]. In an open-label, pilot trial [55], budesonide was administered by jet nebulisation with or without control by the AKITA system to children with asthma. Compared to regular jet nebulisers, the AKITA system achieved similar or better efficacy, and was well accepted by children and their parents. It also reduced the time for inhalation as well as the required nebulised doses [55]. The significance of these results is reflected in a study by Hofmann [56] who found the AKITA system to be an excellent driver of patient adherence, achieving an exceptional 92% adherence rate in children. This also highlighted the usefulness of the logging software of the system for checking patient adherence by doctors and for clinical trials [56]. Beyond adherence, clinical efficacy could also be improved by controlling specific regional deposition. Targeting of small airways in asthma by inhaled medications can be challenging. Therefore, there may be an opportunity to reduce side effects associated with systemic steroid uptake in patients with severe asthma who are not sufficiently controlled using regular inhalation, and systemic steroids are often indicated and associated with side effects. By programming the AKITA system to target the peripheral airways, Janssens and Overweel [57] found that systemic steroid exposure in children with severe asthma was reduced as were hospital admissions.

Other Inhaler Technology
Portable inhaler technology using principles other than those used in pMDIs and DPIs are now entering the market, and are designed with patient ease of use in mind. The development of soft mist inhalers does fall within the definition of a nebuliser, as they transform aqueous liquid solution to liquid aerosol droplets suitable for inhalation. However, at variance with the traditional nebuliser designs, they are hand-held multidose devices that have the potential to compete with both pMDIs and DPIs on the portable inhaler market. At the present, the only soft mist inhaler currently marketed in some European countries is the Respimat® inhaler (Boehringer Ingelheim). This device does not require propellants since it is powered by the energy of a compressed spring inside the inhaler. Individual doses are delivered via a precisely engineered nozzle system as a slow-moving aerosol cloud (hence the term ‘soft mist’) [58]. Scintigraphic studies have shown that, compared to a CFC-based pMDI, lung deposition is higher (up to 50%) and oropharyngeal deposition is lower [58]. Respimat is a ‘press-and-breathe’ device, and the correct inhalation technique closely resembles that used with a pMDI. However, although coordination between firing and inhaling is required, the aerosol emitted from Respimat is released very slowly, with a velocity of approximately four times less than that observed with a CFC-driven pMDI [58]. This greatly reduces the potential for drug impaction in the oropharynx. In addition, the relatively long duration over which the dose is expelled from the Respimat (about 1.2 s compared with 0.1 s from traditional pMDIs) would be expected to greatly reduce the need to coordinate actuation and inspiration, thus improving the potential for greater lung deposition. Although the Respimat has been used relatively little in clinical practice to date, clinical trials seem to confirm that drugs delivered by the Respimat are effective at correspondingly smaller doses in patients with obstructive airway disease [59].

The ‘Bad’ and the ‘Ugly’: Poor Inhaler Technique and Its Consequences
A fundamental requirement that underlies all inhaled therapies is the need to use the inhaler correctly in order to achieve the optimal therapeutic response from the drug. Published evidence shows that, when used correctly, there is little difference in clinical efficacy between different inhaler types [2]. Despite the development of several new and improved types of inhaler devices, there has been no sustained improvement over the past 35 years in patients’ ability to use their inhalers. In fact, several studies have reported that up to 50–60% of patients with asthma or COPD cannot use their inhalers (either pMDIs or DPIs) well enough to benefit from the treatment [23, 60]. These numbers are even more depressing considering that between 40 and 85% of health care professionals, who should readily be able to teach patients how to use their inhalers correctly, do not seem to be able to perform that task properly – and doctors are the worst amongst all health care professionals [61].

Poor inhaler technique has clinical consequences, which have been documented for asthma patients taking inhaled corticosteroids delivered by pMDIs: instability of asthma was more frequent in patients with a poor inhaler technique than in those with a good technique [62]. In a large cross-sectional study involving over 1,600 asthma
outpatients, the finding of just one critical error in the inhalation technique, irrespective of the inhalation device (DPI or pMDI), was associated with increased emergency room visits, hospitalisation and oral medication prescription [63]. More recently, Levy et al. [64] retrospectively evaluated pMDI use in patients with mild-to-moderate asthma and correlated the patients’ inhaler technique with the level of asthma control. Noticeably, the patients’ pMDI inhaler technique was objectively evaluated by using the Vitalograph Aerosol Inhalation Monitor [65], a training device aimed at assessing three crucial steps needed for correct pMDI usage: slow (<50 l/min) inhalation flow; synchronisation between inhaler actuation and inhalation, and a 5-second breath hold pause following inhalation. The authors observed that patients who displayed significant errors when using pMDIs had higher risks of poor asthma control and more bursts of systemic corticosteroid prescriptions than those who operated pMDIs correctly [64]. Of note, patients who were using breath-actuated inhalers had better asthma control than those using pMDIs alone. Synchronisation, i.e. achieving the correct inhalation flow following actuation, was the main step in the inhalation technique which most patients failed [64]. The results of this study confirm the relationship between inhaler misuse and poor asthma control, and reinforce the notion of the importance of patient training for efficient drug inhalation. Patients’ ability to handle inhalers correctly is a crucial issue for the choice of the most appropriate inhaler device for a given patient [1]. Adherence to therapy is likely to be influenced by patients’ attitudes and their experience in using the device, and if the patient feels that their treatment is not working, adherence is likely to be poor, resulting in reduced efficacy of treatment [66]. Evidence shows that patients’ competence in the self-administration of inhaled medications is improved by educational interventions [64], and repeated training in correct inhaler use improves asthma symptoms, quality of life and lung function, and reduces the use of relief medications as well as emergency hospital admissions [66, 67].

A poor inhaler technique also has financial consequences, with one review [67] estimating that about a quarter of all expenses on inhalers is wasted owing to a poor inhaler technique.

Future Directions and Conclusions

In the past 10–15 years, several innovative developments have advanced the field of inhaler design. However, there has been little effort made in that time to systemati-
tient changes, and commit resources for assuring that pa-
ients and caregivers are trained to properly use and main-
tain their devices. Only through recognition of the ‘good’
inhaler we will avoid the ‘bad’ and the ‘ugly’.

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