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Review Article

Theme: Advances in Formulation and Device Technologies for Pulmonary Drug Delivery
Guest Editors: Paul B. Myrdal and Stephen W. Stein

Advances in Metered Dose Inhaler Technology: Hardware Development

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Abstract. Pressurized metered dose inhalers (MDIs) were first introduced in the 1950s and they are currently widely prescribed as portable systems to treat pulmonary conditions. MDIs consist of a formulation containing dissolved or suspended drug and hardware needed to contain the formulation and enable efficient and consistent dose delivery to the patient. The device hardware includes a canister that is appropriately sized to contain sufficient formulation for the required number of doses, a metering valve capable of delivering a consistent amount of drug with each dose delivered, an actuator mouthpiece that atomizes the formulation and serves as a conduit to deliver the aerosol to the patient, and often an indicating mechanism that provides information to the patient on the number of doses remaining. This review focuses on the current state-of-the-art of MDI hardware and includes discussion of enhancements made to the device's core subsystems. In addition, technologies that aid the correct use of MDIs will be discussed. These include spacers, valved holding chambers, and breath-actuated devices. Many of the improvements discussed in this article increase the ability of MDI systems to meet regulatory specifications. Innovations that enhance the functionality of MDIs continue to be balanced by the fact that a key advantage of MDI systems is their low cost per dose. The expansion of the health care market in developing countries and the increased focus on health care costs in many developed countries will ensure that MDIs remain a cost-effective crucial delivery system for treating pulmonary conditions for many years to come.

KEY WORDS: actuator; add-on devices; canister; dose counters; metering valve.

INTRODUCTION TO MDI HARDWARE TECHNOLOGY

Since the commercialization of the first metered dose inhaler (MDI) more than a half century ago, MDIs have become the most widely used delivery system for the treatment of lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). The MDI is readily recognized by the majority of patients who have ever received treatment for asthma in developed countries and, increasingly so, in developing countries. Between 2002 and 2008, 47.5% of inhaled medications sold in Europe were MDIs (1). The relatively low cost (particularly on a cost-per-dose basis) of MDIs and wide variety of medications delivered by MDIs has contributed to the popularity of this delivery system. Indeed, the relatively low cost of MDIs has contributed to a significant growth in MDI use in developing countries and will ensure continued use in developed countries that are facing increased pressure to reduce health care costs (2).

The world's first MDI (Medihaler Epi™; Riker Laboratories which was later acquired by 3M Pharmaceuticals) was initially marketed in 1956 (3). Many of its features are still evident in the hardware of the MDI systems being prescribed today. These include the general form and the key mechanical subsystems (metering valve, canister, and actuator mouthpiece) that make up the device. However, while modern MDIs have much in common with the original MDI, there have been many enhancements of MDI technology. Many of these changes may not be perceived by the average user, but have resulted in significant improvements in product performance characteristics such as dosing reproducibility, delivery efficiency, and product stability.

The principal hardware developments that have recently been introduced, or which are currently being brought towards the market, will be reviewed. As has been the case for MDI formulation development, MDI hardware technology has been significantly advanced as a result of chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) transition and also in response to growing competition from dry powder inhalers. Much of the innovation and improvement of MDI hardware has its roots in the significant corporate investment that began in the early 1990s as the industry transitioned to HFA

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propellants. Innovations in MDI technology continue today and represent an invigoration of a well-proven base technology. In addition, much of the technical innovations of MDI hardware have centered on incorporating novel features that address patients' concerns associated with conventional hardware (4). Primary concerns for using MDIs efficiently include poor coordination of inhalation and actuation, inhaling too quickly or too slowly, high oropharyngeal deposition, and patients not knowing when to replace their MDI.

MDI VALVE DESIGN AND INNOVATION

It is appropriate to start any review of MDI hardware with the metering valve, as it is the heart of the system and is of greater complexity than any other hardware subsystem. The basic function of any metering valve is to ensure that a consistent amount of formulation (and ideally drug) is released from the canister each time the patient actuates the device. In order to do this in a way that enables meeting regulatory requirements on dosing uniformity, the valve must meet two critical criteria. First, the valve must release a consistent total mass of the bulk formulation in each actuation. Secondly, the valve must uniformly sample from the bulk formulation such that the concentration of drug in the sampled volume is representative of the concentration of drug in the bulk formulation.

In a sense, an MDI valve acts as two separate valves, one at either end of the metering chamber. The outer valve (which seals the system from the outside world) is kept closed while formulation is allowed into the metering chamber. The inner valve then closes, isolating a single dose of the correct volume from the bulk of formulation in the MDI canister. Once the correct volume has been sampled, the outer valve is then allowed to open, dispensing the dose under the vapor pressure of its own propellant. The outer valve then recloses and the inner valve then reopens, in preparation for the next dose.

In addition to these fundamental steps, the metering valve must also meet a long list of other criteria. These include accurate metering of the formulation, acceptable sampling of suspension formulations, low leakage during storage, low moisture transmission, low actuation forces, low extractables, low leachables, low drug uptake, low drug degradation, and low particulate generation. Metering valves must also be simple, reliable, and cheap.

Conventional MDI Valve Designs

Traditionally, MDI metering valves have been of a press-to-fire design with a protruding male valve stem being depressed inwards towards the canister to dispense a dose. In reality, it is the canister that is pushed down relative to the valve stem. At rest, the inner valve is open and the outer one is held closed by an internal compression spring that returns the valve stem to this position after the patient has taken a dose. An example of such a valve is the Spraymiser™ valve design shown in Fig. 1. When the ferrule is crimped onto the canister, the ferrule gasket provides a seal between the canister and the valve. The performance of the ferrule gasket and the diaphragm determine the rate of leakage of propellant out of the canister. The seal properties also influence the rate of moisture ingress into the formulation.

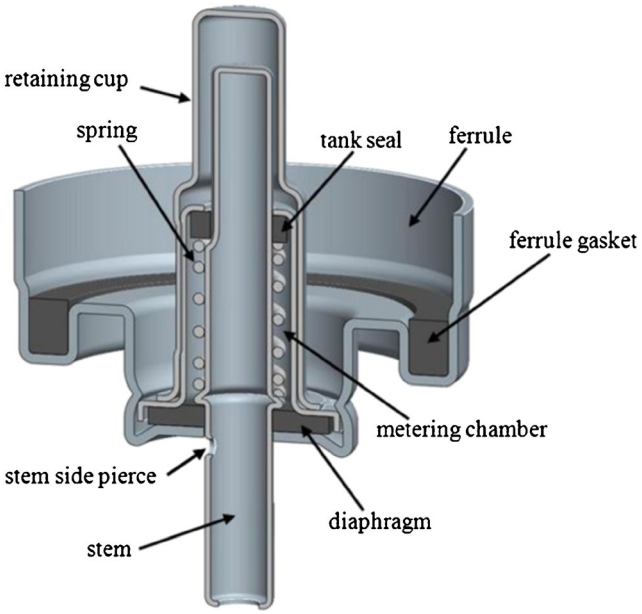

Fig. 1. Schematic of the Spraymiser™ valve

During final assembly, the valve stem is inserted into the actuator nozzle block and couples the canister to the actuator. The valve stem acts as a conduit through which the formulation passes as it exits the metering chamber and flows into the expansion chamber and then out of the actuator nozzle. As the valve stem is depressed slightly, the groove (or the orifice in the case of some other valves) in the valve stem passes through the tank seal, thus sealing the metering chamber and defining the formulation to be delivered during dosing. The volume of formulation delivered with each dose typically has a target value between 25 and 100 μL. As the valve stem is further depressed, the valve stem side piercing passes through the diaphragm and enters into the metering chamber and the formulation is discharged from the metering chamber due to its high pressure. The fit between the valve stem and the openings in the diaphragm and tank seal are optimized in order to minimize leakage while maintaining the force required to actuate the dose at an acceptable level.

Many MDI valves include an enclosure, referred to as a retaining cup, around the components associated with forming the metering chamber and releasing the dose (see Fig. 1). The purpose of the retaining cup is to prevent formulation from draining out of the metering chamber when the valve is stored in an upright position (3). The retaining cup has a gap at the top that allows formulation to pass through the retaining cup and into the metering valve when the MDI is in the inverted position (the position when the patient administers a dose and thus when the metering valve refills for the next dose). Retaining cups are required for many valve designs in order to avoid unacceptable "loss of prime" (LOP) behavior upon storage with the valve in the upright position. In addition, retaining cups provide greatly enhanced consistency of delivery as the canister is approaching the end of the labeled number of doses (see Fig. 2) (5).

When CFC to HFA transition started to occur, the main MDI metering valve manufacturers (3M, Bespak and Valois) adapted their existing valve designs to suit the new propellants and cosolvents. Primarily, this involved developing new

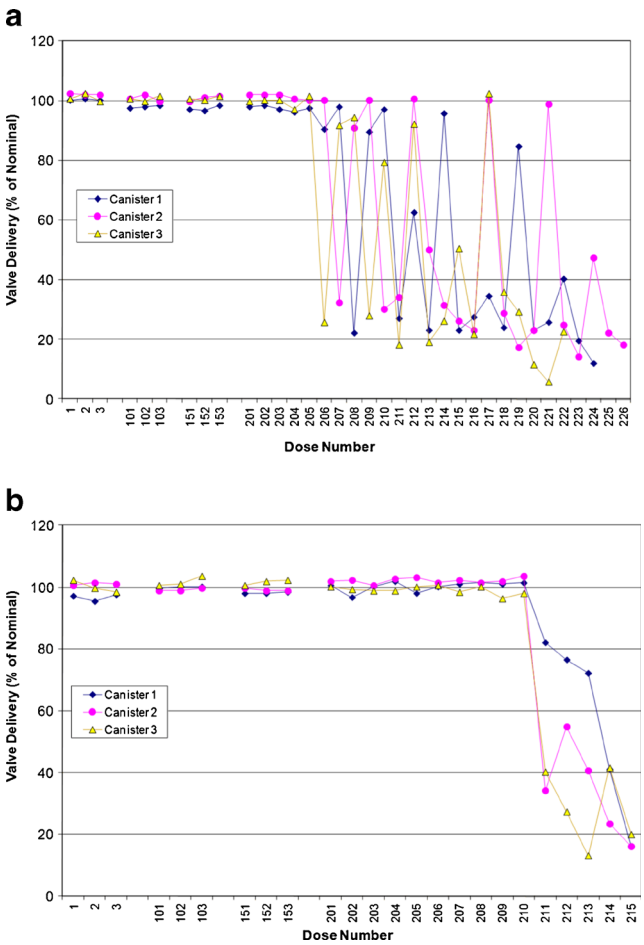

Fig. 2. **a** Formulation delivery for a CFC albuterol MDI. **b** Formulation delivery for a HFA albuterol MDI. Adapted from Ross and Gabrio, 1999 (5)

rubbers (typically ethanol-extracted ethylene propylene diene monomer—EPDM, nitrile, or chloroprene rubbers) for the seals. As a result, HFA MDIs have been developed using the same press-to-fire valve designs.

Alternative Valve Designs

While conventional MDI valve designs are often adequate, shortcomings of conventional MDI valves have been identified as the requirements of product developers and regulatory authorities have become more strenuous. LOP, imperfect sampling of suspension formulations that flocculate rapidly, drug accumulation in restricted corners as a result of vibration during transportation, drug uptake on valve components, drug degradation, and generation of unwanted particles are issues that must be avoided. These challenges have led to numerous improvements in valve designs.

LOP can be caused in several ways. One principle cause is loss of liquid from the metering chamber due to "shake-out" by the patient. Alternatively, vapor bubbles may form in the metering chamber during prolonged storage or temperature cycling, or air can replace some of the residual vapor in the metering chamber while the valve is in its firing position. This vapor or air may then not be completely displaced by liquid formulation when the next dose is metered. Two very different valve design strategies have been utilized to avoid LOP as well as problems sampling suspension formulation. One strategy is to make the inlet passageway(s) to the valve narrow and tortuous, and/or to close them off at rest with an additional seal. An example of a commercially successful valve that takes this "dose retention" approach is the Valois DF30 valve. A second, essentially opposite strategy is to design valves with much more open inlet passageways. Examples include Bespak's Easifill™ valve (Fig. 3), the 3M Face Seal Valve™ (Fig. 4) (6) and Valois' ACT valve. Such "free flow" or "fast-fill, fast-empty" (FFFE) valves work on the principle that access to the metering chamber is sufficiently open and unrestricted such that the liquid formulation readily displaces any accumulated air or vapor bubbles. Proper shaking is still required to ensure that suspended particles are uniformly distributed throughout the system. One concern with FFFE valves is the potential of increasing dose through the life of the MDI, which may occur when a dose is not completely delivered (7). Since the metering chamber is open to the bulk of the formulation, the partial dose that is not delivered can wash back into the bulk, causing a rise in the drug concentration. Alternatively, poor suspension quality (e.g., creamed formulations) can also contribute to this problem. This effect is more pronounced for slow creaming suspension and concentrated solution formulations compared to fast settling suspension and dilute solution formulations. Carefully designed sediment collectors (8,9) have been devised to provide additional protection, if required, against sedimentation into the region around the valve inlet. Such FFFE design concepts remove the need to prime before use and are less sensitive to patient use technique. Other FFFE design concepts have been proposed (10).

Concepts for improving FFFE valve designs include using a "virtual" metering chamber that forms only as the valve is

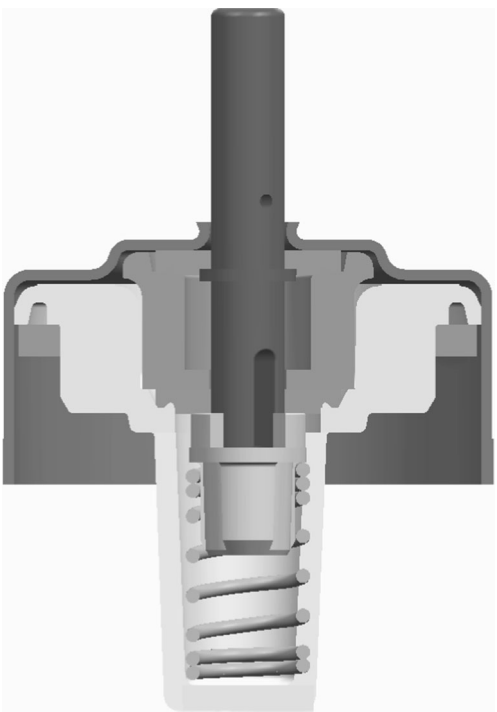

Fig. 3. The Easifill™ valve, which fills via open channels in its stem. Drawing courtesy of Bespak plc

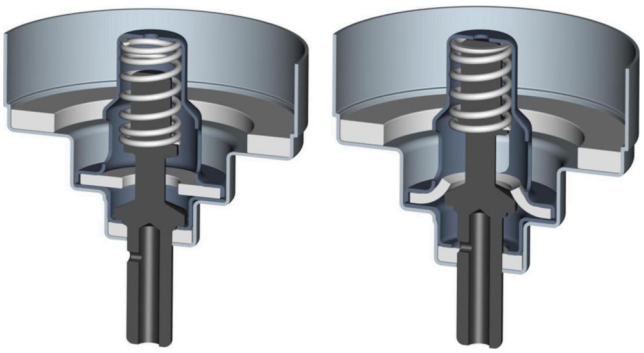

Fig. 4. A schematic of the 3M Face Seal Valve™ utilizing a virtual metering chamber. The drawing on the *left* shows the valve in the "at rest" position; the drawing on the *right* shows the valve in the "during actuation" position. Drawing courtesy of 3M Healthcare Ltd.

actuated (11). This works on the principle that the metering chamber volume is almost zero at rest, eliminating the concerns about loss of formulation or migration of drug in and out of the metering chamber during shaking or storage. Further related valve designs have been patented (12,13). Other hardware features devised to improve the consistency of sampling of suspensions include parts that move to improve homogenization of the formulation as the MDI is shaken (14).

Some other unique valve designs are also being investigated. Namely, Chiesi Farmaceutici S.p.A. is developing a valve that can deliver two different drugs, sequentially, from one MDI canister (15). The canister is designed to have two formulation reservoirs, one within the other, that contain two different formulations. Upon actuation, the metering valve is designed to deliver the first metered dose from the first formulation (outer reservoir) and the second metered dose from the second formulation, which is housed in the inner reservoir. Typical MDI valves are designed to deliver between 25 and 100 μL of formulation per actuation. In order to deliver high doses of drug, it would be desirable to utilize larger valve sizes. However, a challenge with this approach is that the efficiency of the drug delivery decreases as the size of the valve increases (16). During dose delivery, the propellant expands to continuously fill the volume of the expansion chamber causing the propellant to cool. This leads to a decrease in the vapor pressure, and thus limits the delivery efficiency that can be obtained with large valves. In order to overcome this limitation, a novel valve has been envisioned that uses a built-in "pressurizer" to apply pressure to the formulation within the metering chamber while the formulation is being released from the metering chamber (17).

Valve Materials and Coatings

A typical MDI valve consists of three elastomeric components, a metal spring, a metal ferrule, and the remaining components which can be either metal or a molded plastic. An advantage of molded parts is that they allow for increased flexibility in part design compared to the drawing process used to form metal components. Advantages of metal components include lower cost, reduced temperature cycling effects (18), and reduced moisture ingress into the formulation for metal valve stems. Increased regulatory requirements on dosing uniformity and on extractables and leachables have resulted in changes in the materials used in valve components. Cleaner elastomers continue to be developed for use in MDIs. Unextracted nitrile rubber components have been replaced by pre-extracted components. EPDM rubbers have been introduced in order to reduce extractables and leachables levels. Clean thermoplastic elastomers (TPEs) (19) are being employed as canister sealing gaskets. While the use of TPEs as dynamic valve seals has not yet proved possible, due to the creep properties of such materials, it is likely that materials will be developed for valve seals that have improved cleanliness, reduced drug uptake, and reduced swell in formulation. In addition to providing acceptable extractables and leachables profiles, the elastomer must be optimized to account for any swelling of the elastomer that occurs after exposure to the formulation. Elastomer swelling is highly formulation dependent and is usually lower using EPDM elastomers compared to nitrile elastomers. Elastomer swelling can cause changes in the force profile and metering volume of the valve.

Surface coatings are being developed for valve components in order to reduce drug deposition on the valve surfaces and to reduce the friction between the moving parts of the valve. The highly electronegative mantle of HFAs leads to strong interactions between the drug and other drug particles or surfaces (20). This can lead to significant particle deposition on the canister or valve surfaces. Coating the surfaces of valve components is more challenging than coating canisters due to the intricate geometries of these components and the tight dimensional tolerances needed in order to achieve acceptable valve performance. As a result, the use of fluoropolymer-based lacquers is not suitable for valve coatings. Additionally, the high temperature of the curing process limits the utility with molded plastic valve components (21). Plasma-based coating technologies are more suitable for providing dimensionally insignificant coatings on valve components. A dual-layer coating less than a micrometer thick, consisting of a vapor deposited inorganic layer and a fluorine layer, has been shown to greatly reduce friction and drug deposition in HFA formulations using both metal and plastic valves (21,22). Other approaches for providing valve components with low surface energy have been described including an approach for providing a monolayer surface treatment by exposing metal components to an organic surface treatment that covalently bonds to the metal surface (23).

Silicone oil is a common valve lubricant utilized in MDIs and has been found at levels between 50 and 350 μg per valve (24). Depending on the method of application of the silicone oil to the MDI valve and method of storage of the canister, the oil may leach into the liquid formulation and cause particle growth over time, thus impacting the overall performance of the MDI. Storing the canister upright orientation has been shown to cause less particle coarsening than if the canister is stored inverted (25). In a study by Fallon *et al.* (24), commercial HFA 134a (1,1,1,2-tetrafluoroethane) suspension MDI formulations were spiked with 200 to 550 μg silicone oil. With the addition of silicone oil, the mass median aerodynamic particle size (defined as aerodynamic diameter at which 50% of the aerosolized mass lies below the stated diameter, MMAD) increased from 2.60 μm to 2.62 and 2.68 μm for the formulations with 200 and 550 μg silicone oil, respectively. For

HFA 227 (1,1,1,2,3,3,3-heptafluoropropane) steroidal suspension formulations, increasing the amount of valve lubricant was shown to increase the amount of silicone oil found in the formulation and cause particle coarsening, which affected the fine particle fraction (the mass of aerosol particles delivered from the device with aerodynamic diameters that are approximately less than 5 μm divided by the total mass of drug delivered from the device, FPF) (25,26). The change in particle size distribution over time was attributed to the drug product having an increased propensity to aggregate in the presence of silicone oil.

MDI CANISTER DESIGNS AND INNOVATION

Improved canisters are also being utilized in new and future MDI products. Canisters are typically made from metals such as aluminum or stainless steel, but glass canisters have been used as well. The size of the canister depends on the size of the valve to be utilized as well as the total number of doses to be administered. The typical canister volume is about 10 to 20 mL. The most widespread recent innovation on MDI canisters is the introduction of new internal coating materials, usually incorporated to minimize formulation–canister interactions. Some solution formulations are susceptible to catalytic degradation in the presence of aluminum (27,28). Many HFA suspension formulations are susceptible to drug deposition on the canister surfaces (20–22). Surface coatings are utilized to overcome these formulation challenges. In particular, low-energy surface coatings are widely used in order to reduce unwanted drug deposition on the surface of the canister. Examples being developed include fluorinated ethylene propylene, perfluoroalkoxyalkane, and related materials and blends (16,27,29,30). In addition, non-fluorinated materials, such as submicron layer of fused silica glass (31), anodized aluminum, and epoxy-phenolic resin (32), are also being investigated as potential coatings for aluminum canisters. Internally coated canisters are now commercially available from Presspart, 3M, and Intrapac, among others. Other coating approaches are being developed as well that provide thinner coatings (21,23,33,34); however, obtaining thin coatings is not as critical for the canister as it is for valve components. Other canister technology now available includes improved plastic-coated glass bottles (e.g., Schott AG's Purgard™ system) and reduced headspace canisters with external metal sleeves to fit standard actuators (35). The latter designs are a response to market trends towards smaller numbers of doses per inhaler. Whereas 200 or more doses used to be standard, 60 to 120 is becoming the norm for new asthma and COPD drugs, sometimes with 30 dose sample packs for the USA market. In the future, still smaller canisters (36,37) may be required for treating other therapeutic indications.

MDI ACTUATOR DESIGN AND INNOVATIONS

The MDI actuator is a key subsystem that significantly influences the delivery characteristics of an MDI. Figure 5 shows a schematic of a typical press-and-breathe MDI actuator. The atomization of the formulation is significantly influenced by the atomization orifice (sometimes referred to as "spray nozzle"). The actuator sump, the valve metering chamber, and volume of the valve stem that the formulation flows through after exiting the valve side pierce form an "expansion chamber," which also impacts the atomization. The actuator nozzle block contains a ledge that fixes the position of the tip of the valve stem. It is critical that the nozzle block fit tightly around the valve stem in order to prevent leakage of the formulation during the atomization event. On the other hand, the fit must not be so tight that the valve stem cannot be inserted into the nozzle block without discharging a dose. The atomized aerosol is delivered to the patient through the actuator mouthpiece which can influence the efficiency with which the atomized droplets penetrate the patient's oropharynx.

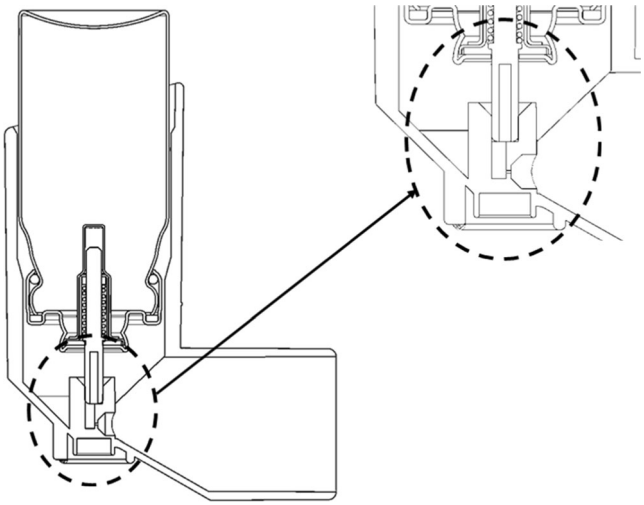

Fig. 5. Schematic of an MDI press-and-breathe actuator. Drawing courtesy of 3M Healthcare Ltd.

While in many respects MDI actuators are quite similar to the original designs, numerous improvements have been evaluated and implemented. Many of these improvements focus on the desire to improve the drug delivery by (1) modifying the nature of the atomized spray, (2) manipulating the disposition of the atomized particles, and (3) improving patient coordination. Most press-and-breathe MDI actuators are molded out of plastics such as polypropylene or high-density polyethylene. Materials providing novel properties may be utilized in the future, but the material selection is significantly influenced by regulatory considerations, particularly extractable and leachable propensities. Key aspects of MDI actuators will be described in further detail.

Influence of Spray Nozzle Design

The aerosol formation that occurs when the patient discharges the device is a highly dynamic and complex process. Once the valve stem is depressed, the propellant-based formulation exits the valve-metering chamber through the side piercing in the valve stem and flows through the expansion chamber and out of the spray nozzle. This process has been described in great detail elsewhere (38–40). In addition to formulation parameters, the actuator nozzle orifice diameter (OD) significantly influences the dynamics of the atomized spray (38–42). The valve metering volume and the diameter of the valve stem side piercing also influence the dynamics of delivery (38,42). Figure 6 shows the influence of the OD and valve delivery on the FPF delivered from Andersen cascade

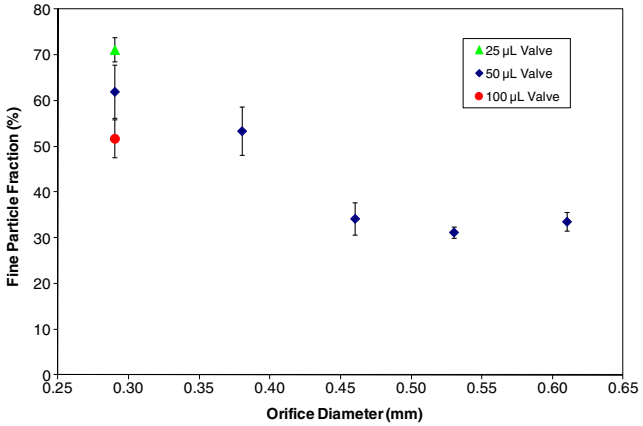

Fig. 6. The influence of valve size and nozzle orifice diameter on the fine particle fraction delivered using HFA 134a solution formulation of 0.167% (w/w) beclomethasone dipropionate and 8% (w/w) ethanol

impactor testing of HFA 134a formulations containing 0.167% (w/w) beclomethasone dipropionate (BDP) and 8% (w/w) ethanol. The most efficient delivery is obtained using small ODs and low valve sizes. Interestingly, HFA 227 suspension MDIs showed a similar increase in FPF with decreasing OD, but the size of the metering valve did not have significant influence on the product performance.

The FPF delivered from various MDI formulations has been shown to increase with decreasing OD (42,43). This increase in FPF is driven primarily by a decrease in the momentum of the plume for smaller ODs which, in turn, leads to a decrease in deposition in the United States Pharmacopeia (USP) inlet or oropharynx (41).The OD also influences the initial diameter of the atomized droplets slightly (44). A previous study examined four different HFA 134a solution formulations tested with three different valve sizes and actuators with ODs ranging from 0.29 to 0.49 mm (45). In this study, the average initial droplet diameters increased by only about 10% as the OD increased from 0.29 to 0.49 mm.

While decreasing OD is desirable from a drug delivery standpoint, there are practical limits on how small the OD can be. Lewis *et al.* (46) demonstrated that the FPF of an HFA 134a solution formulation containing 0.45% (w/w) BDP, 15% (w/w) ethanol, and 1.3% (w/w) propylene glycol could be increased from 19% with an OD of 0.42 mm to in excess of 70% at ODs less than 0.14 mm but at the expense of increased plume duration (greater than 1 s for 0.14 mm OD compared to about 200 ms for 0.42 mm OD). Improvements in delivery associated with decreased ODs are thus limited due to the need to accommodate the limited duration of typical patient inhalation profiles. Nozzle blockage also becomes problematic when small actuator ODs are used. Thus, while decreasing OD is desirable from a drug delivery standpoint, commercialized MDI products to date have all had OD of about 0.3 mm or greater.

The influence of spray nozzle shape and design has also been investigated in significant detail. Nozzle configurations including multiple nozzles, slot nozzles, cross-shaped nozzles, and other nozzle shapes have been evaluated *in vitro* and found to result in no improvement in the FPF relative to conventional round nozzle geometry of similar cross-sectional area (47). This may be due to the fact that visualization of the atomization in HFA systems has indicated that the atomization appears to occur at the exit of the spray nozzle (46). Actuators with spray nozzles that swirl the emerging spray are well known (48), but more recent examples of patented systems include a vortex nozzle system from Kos Pharmaceuticals (49–51). The benefit of such novel spray nozzles has been readily established for the atomization of other lower volatility fluids (52), but has not yet been clearly established for HFA-based MDIs. Kakade *et al.* (51) did show a slight increase in the delivery efficiency from an actuator using a vortex nozzle compared to two commercial actuators using conventional nozzles.

Various nozzle exit geometries have been incorporated into MDI actuators and can significantly influence performance. Often the exit of the nozzle is in the shape of a cone; however, numerous other exits, such as flat and spout geometries, have been evaluated (53,54). A "double-cone" nozzle configuration (in which a smaller inner cone and a larger outer cone with a short cylindrical distance between them) was shown to significantly reduce the width of the spray and increase the droplet diameter measured via laser diffraction (54). A recent study indicated that nozzle exit geometry can impact on the electrostatic charge of the atomized particles. Not only does the geometric difference between flat and cone nozzle impact the electrostatic charge carried by the aerosol particles but the presence of a very small radius on the exit of the orifice significantly influenced both electrostatic charge and drug delivery. Chen *et al.* (55) evaluated triboelectrification and mass deposition of BDP HFA 134a formulations (containing 15% w/w ethanol) from sharp-edge and curved-edge nozzle designs for flat and cone polytetrafluoroethylene (PTFE) actuator nozzles using a modified electrical low-pressure impactor and the USP inlet. PTFE tends to charge negatively with friction between an aerosol plume and the nozzle due to the electronegativity of the fluorine atoms. It was noted that all four nozzle geometries produced the similar particle MMAD results, but the mass deposited on the USP inlet was consistently higher for actuators with the curved edge at the orifice exit compared to those with a sharp edge at the orifice exit.

The Influence of Sump Volume

The expansion chamber volume, which is comprised of the volume of the actuator sump and the internal valve stem bore, can influence the ratio of propellant in the liquid and vapor phases during the atomization process (38–40,56–59) and thus has the potential to influence drug delivery. However, in practice the influence of sump volume on delivery is minimal since the sump contributes only a small fraction of the overall expansion chamber volume (46). Lewis *et al.* (46) examined the influence of sump volume on the drug delivery from solution formulation of BDP containing 8% ethanol in HFA 134a and found no difference in delivery when sump volume was varied by a factor of two. Similarly, Dunbar and Hickey observed negligible differences in drug delivery for a 6-fold increase in sump volume (42).

The Influence of Mouthpiece Configuration and Airflow Manipulation

The plume leaving the exit nozzle is highly dynamic and rapidly changes in droplet size, composition, and velocity

(38–40,56). The disposition of these droplets depends on a number of factors including the nature of the initial atomized spray (e.g., the initial droplet size, velocity, spray angle, and the overall plume momentum). However, the actuator mouthpiece configuration and the flow that it induces can also significantly impact the particle disposition. By increasing the mouthpiece length, drug deposition that would otherwise occur in the USP inlet can be transferred to the mouthpiece (46) much in the same way a spacer works. In this way, the mouthpiece collects droplets that would otherwise collect in the oropharynx due to the high turbulent intensity in this region (60). The shape of the actuator mouthpiece may also influence the shape of the patient's oral cavity during inhalation which can also impact deposition profiles. Lin *et al.* (61) showed that deposition in human airway replicas was decreased as mouthpiece diameter increased from 1.5 to 2.7 cm indicating that improved delivery can be obtained using larger mouthpiece diameters. The decrease in oropharyngeal deposition was generally most significant for larger particles and at higher inhalation flow rates.

Novel actuator designs have been developed to manipulate the airflow in the actuator mouthpiece with the objective of decreasing oropharyngeal deposition by reducing the velocity of the droplets exiting the mouthpiece. The Tempo™ inhaler system (MAP Pharmaceuticals Inc.) reduces the airflow momentum using an opposing air jet system (62). Additionally, a porous mouthpiece is used to allow air to flow perpendicular to the mouthpiece in order to reduce deposition in the mouthpiece. A system from 3M has been shown to greatly reduce the momentum of the plume by restricting airflow in the vicinity of the spray nozzle during the aerosolization process (63). Other similar systems include the Gentlehaler™ (64) from Schering-Plough and an actuator from Bespak (65) in which the incoming air is made to swirl in an opposing vortex that slows the aerosol spray. These systems offer the benefits of slower, gentler sprays, and therefore a reduction of the unwanted deposition of drug in the patient's oropharyngeal region. However, these approaches for slowing down the plume result in significant airflow turbulence in the mouthpiece which leads to increased mouthpiece deposition as well as increased complexity and cost of the device. Shrewsbury *et al.* (66) describe delivery from a scintigraphic evaluation of a CFC fluticasone propionate formulation (Flovent®) in which the Tempo™ inhaler increased lung deposition from 14% to 42% compared to a standard press-and-breathe actuator, but actuator deposition was increased from 9 to 39%. An *in vitro* evaluation of the same formulation showed an increase in delivery efficiency from 34% to 54% by using the Tempo™ inhaler with an increase in actuator deposition from 15% to 44% (67).

Breath Actuation

One of the biggest challenges associated with effective lung delivery using MDIs is the difficulty some patients have actuating the device at the appropriate point in the inspiratory cycle (68,69). Lung deposition is reduced (sometimes, greatly) when the patient actuates the device before or after inhaling (70). Young children and elderly individuals have a particular difficulty coordinating inhalation and actuation of the device. One approach to overcome this problem is to utilize breath-actuated MDI actuators. Leach *et al.* (71) and Newman *et al.* (70) observed that lung deposition from the patients using the 3M Autohaler™ device was essentially identical to lung deposition for patients with good coordination using a press-and-breathe MDI of the same formulation, but was significantly higher than that for patients with poor coordination using a press-and-breathe MDI. Numerous studies have shown improved deposition and increased patient confidence that a dose was successfully delivered associated with the use of breath-actuated delivery (70,72,73). Overall, incorporating breath-actuated inhalers into patients' regimen may improve overall disease control and reduce health care costs associated with asthma or COPD compared to conventional MDIs (74) in spite of increased device cost and complexity.

The Autohaler™ (Fig. 7) was the first breath-actuated MDI system and was commercialized by 3M Riker in 1970 (3). The IVAX Easi-Breathe™ device (developed by Norton Healthcare) is similar in function to the Autohaler™, but automatically prepares the device for use when the patient opens the mouthpiece cover (75). Patients who used Maxair Autohaler™ achieved greater pulmonary drug deposition than did patients who had poor coordination while using conventional MDIs (74). Other breath-actuated devices available include Meridica's system based on a cascade of collapsing knee joints (76), Cambridge Consultants' mechanical system (77), and an automatically resetting pneumatic system under development by Kos (78). In addition, less sophisticated breath coordination systems have been devised (79) in which either the patient is prevented from mechanically depressing the canister until he/she inhales or patient inhalation is blocked until he/she depresses the aerosol canister. Although slightly more complex for the patient, such systems have the advantage (for the developers and manufacturers) in that they do not tend to impose any additional requirements on the metering valves. The MD Turbo™ by Respirics was developed as an independent device designed to fit a variety of commercially available MDIs. A system (80) that offers an interesting alternative approach is the K-Valve™ (Fig. 8) which is a breath-actuated secondary valve formed as a kink in a plastic tube. The patient presses the canister downwards to release a metered dose from the primary valve in the usual manner, but the aerosol of the medication is then held in the plastic tube until the patient's inhalation moves a vane that unkinks the tube.

At the other end of the scale of complexity are several electronic-based breath-actuation systems. Devices developed to an advanced state include Aradigm's SmartMist™ device (81), which is no longer promoted, that used a miniature pneumotachograph to trigger drug delivery at the appropriate point during the inspiratory maneuver (82) and GW Pharmaceuticals' Advanced Dispensing System for cannabinoids (83), which has a large number of usage pattern monitoring and control capabilities, among other features.

USE OF ADD-ON DEVICES WITH MDIs

Spacer and add-on devices are sometimes used with MDIs as a means of improving delivery. Add-on devices can improve delivery by intercepting and therefore removing coarser particles that would otherwise collect in the oropharynx, increasing the FPF by providing increased time for the

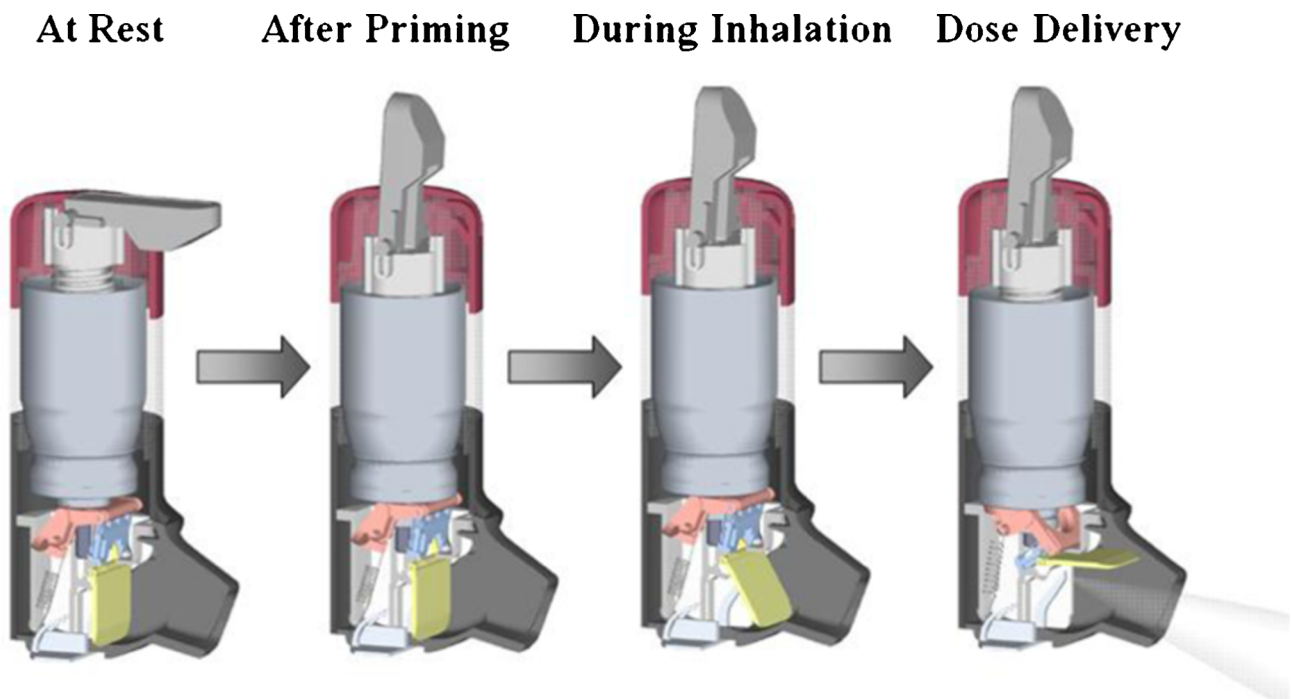

Fig. 7. Schematic of the 3M Autohaler™ breath-actuated inhaler. During priming, a spring is compressed and pushes on the canister, but the canister is prevented from moving by the rocker (in *pink*) which is held in place by the catch (in *blue*). During inhalation, the patient airflow moves a vane (in *yellow*) which releases the catch and allows for the rocker to rotate. At this point, the energy stored in the spring during priming depresses the canister relative to the valve and the dose is discharged to the patient. Drawing courtesy of 3M Healthcare Ltd.

droplets to evaporate and slow down, or reducing the sensitivity of delivery on patient coordination of inhalation and actuation. Various types of add-on devices have been developed. Using the nomenclature proposed by Dolovich (84) and adopted by Newman (85), these include "spacers" which are simply extensions of the MDI actuator mouthpiece, "holding chambers" which are extensions (often larger in volume) that contain a one-way inhalation valve, and "reverse flow devices" in which the spray is actuated in the direction away from the patient's body and into a chamber that is subsequently emptied through a mouthpiece port by the patient inhalation. Add-on devices are typically developed independently of the MDI and are prescribed by physicians in conjunction with MDIs. The significant bulk associated with add-on devices has greatly limited their use since patients prefer readily portable inhaler systems. In order to overcome this, collapsible spacers have been integrated into the MDI actuator (such as an integrated spacer developed by Forest Laboratories).

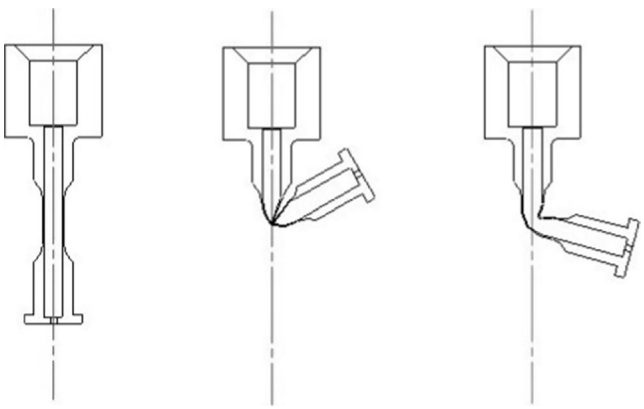

Fig. 8. Schematic of the K-Valve™ breath-actuation system. The image to the *left* shows the plastic tube at rest (the valve tip would be inserted at the top of the open tube). The *middle* image shows the plastic tube in the "kinked" position which occurs after the patient depresses the canister to retain the metered dose. A breath-actuated triggering system is then used to un-kink the tube to release the dose as shown in the image on the *right*. Drawing courtesy of Clinical Designs Ltd.

Numerous studies have shown that the reduced oropharyngeal deposition of inhaled corticosteroids when add-on devices are used can result in decreased systemic side effects (86,87). Large volume spacers and holding chambers allow for MDIs to be actuated prior to patient inhalation, avoiding the need to coordinate actuation and inhalation. Increasing delay time between firing and inhalation and firing multiple actuations into the device results in increased deposition of drug in the add-on device and thus decreases the delivery efficiency (88). The geometry of the spacer also impacts the amount of drug deposition (89). Electrostatic charge on the surface of the add-on device can decrease the efficiency of drug delivery (88,90). A detailed discussion of add-on devices can be found elsewhere (85).

DOSE COUNTERS AND CONTENT INDICATORS

The patient's desire for some form of content indicator or dose counter has long been recognized (91) due to the difficulty that patients have in determining when the MDI should be replaced. In a study assessing patients' satisfaction with current MDIs, 52% of patients reported that they are extremely unsure and 10% are somewhat unsure of how much

medication remains in their current rescue inhaler. With the addition of an integrated dose counter, 97.4% of patients reported that they could tell when to replace their inhalers (92). A complicating factor is the fact that MDIs require that a significant amount of excess formulation (often 20–30 doses worth) be filled into the canister during manufacturing. Once the labeled number of doses for a MDI has been delivered and the MDI begins delivering the excess formulation, the delivered dose can become erratic. While end-of-life profiles for HFA valves are significantly improved compared to older CFC valves (5), it is still difficult for the patient to know when the dose delivery from the MDI has become compromised. This is particularly important for MDIs delivering drugs, such as albuterol, that are used to treat acute asthma attacks. As a result, various approaches have been proposed and developed for helping the patient know when to replace his/her MDI.

Patients utilize a variety of approaches for deciding when to discard an inhaler including determining if the canister floats, shaking the canister, counting doses on a piece of paper, test-firing the inhalers, and evaluating the taste or feel of the spray, among others. Holt *et al.* (93) described a survey of 17 patients using Ventolin® MDIs and reported that 15 of the 17 subjects determined when they needed to replace their inhaler at least in part by shaking the MDI, two of the subjects test-fired the inhaler, one of the subjects determined if the canister floated, and one subject looked for changes in taste. In a separate study, 100 patients returned Ventolin® MDIs that they deemed to be ready to discard (93). Gravimetric evaluation of the returned units indicated that 84% of the MDIs had been actuated more than the labeled number of actuations (93). On the other hand, approximately 11% of the units returned in this study had at least 40 doses remaining. This study demonstrates the difficulty patients have discerning whether or not doses remain in MDIs that do not have some type of dose indication system.

Systems have been proposed ranging from clear canisters that allow the patient to see if there is formulation remaining in the canister to electronic dose counters with built-in compliance monitors that keep track of when doses have been taken or even indicate to the patient that a dose must be taken. Contents indicators refer to features that provide feedback to the patient on the amount of formulation remaining in the device, but do not provide an assessment of the number of doses remaining in the unit and thus provide limited information to the patient. Examples of content indicators include plastic-covered glass canisters, built-in balance systems (94), or floating internal rattles (95). While these dose indicators provide some information to the patient, the patient can easily misinterpret the indicator. As a result, they have not been readily adopted and are not deemed acceptable by many regulators (96). Dose counters, on the other hand, provide an actual representation of the number of doses remaining in the device and are thus preferred. GlaxoSmithKline launched the first dose counter fitted MDI product (the Seretide™ Evohaler™) in 2004.

While the need for dose counters has been long acknowledged, the amount of innovation in dose counters has greatly increased since the United States Food and Drug Administration (FDA) issued a guidance document (97) in 2003 requiring the industry to implement plans for the introduction of dose counters onto MDIs. The key requirements from this document are summarized below:

1. Dose counters should provide a clear indication of when the MDI is approaching the end of the labeled number of actuations as well as when it has reached or surpassed this number.
2. The indication to the patient that he/she is approaching the end of the labeled number of actuations must occur early enough to provide the patient time to obtain a new MDI.
3. If a numeric count is used, the device must count down from the labeled number of doses to zero (with zero indicating that no doses remain).
4. The reliability of the dose counting mechanism should be as close to 100% as possible.
5. If some low frequency of error is unavoidable, the device should specifically avoid undercounting since it could lead to the dangerous situation of the patient thinking that doses are available when the MDI is actually empty.
6. The reliability of a dose counter must be demonstrated *in vitro* (simulating both use and potential abuse) as well as in clinical use.
7. MDIs may includes a "lock-out" feature that prevents delivery of doses after the labeled number of doses has been delivered, but this must not be used for rescue bronchodilators.

The MDI dose counters under development themselves offer a wide range of different approaches. An ideal dose counter directly measures whether a dose has been delivered, for example by measuring a decrease in mass of the inhaler or the flow of fluid out of the nozzle. However, this approach is currently prohibitively expensive and as a result, most dose counters under development measure something linked with the event (98). Current MDI dose counters generally fall into two categories: (1) force-driven counters and (2) displacement-driven counters. The key challenge in designing force-driven counters is matching the force associated with advancing the dose counter to the force required to actuate the valve. In order to avoid undercounting (a critical requirement of the FDA Guidance), it is necessary to set the force to count slightly below the lower limit of the force to fire the valve. Similarly, for displacement-driven counters, the distance required to advance the counter must be designed to be slightly less than the minimum displacement required to fire the device. Thus, for both approaches, it is necessary to design the dose counter in such a way that the dose counter may overcount if the canister is depressed with enough force or displacement to advance the counter but insufficient force or displacement to fire a dose. Thus, control of the force and displacement required to fire the valve from lot-to-lot is critical for good dose counter function. Bradshaw (98) concluded that variability in the force required to advance the dose counter is actually a more significant factor limiting the accuracy of force-driven counters than is variability in valve forces and that force-driven counters are more likely to undercount than are displacement-driven counters. However, the practical significance of this with patients has yet to be established. In a study of the Ventolin® HFA integrated displacement-driven dose counter, a discrepancy rate between the dose counter and patient diary-recorded actuations of 0.76% was observed in 43,865 actuations (99). The incidence rate of undercounts in this study was 0.09%. A study of the integrated

dose counter performance for Advair® HFA showed a similar miscount rate of 0.94% and an undercount rate of 0.13% (100). A study of the integrated dose counter used in Dulera® MDIs yielded a lower total miscount rate of 0.13% and an undercount rate of 0.05% (101,102).

An example of a commercially available force-driven dose counter is the top-mount actuation indicator, AeroCount® from Trudell Medical International (96) (see Fig. 9). Examples of displacement-driven dose counters currently available are the Valois Pharma Landmark™, GlaxoSmithKline Evohaler™ dose counter, and the 3M™ Integrated Dose by Dose Counter (103). Others have also been proposed (104). An excellent summary of MDI dose counters can be found elsewhere (98).

When it comes to the nature of mechanical counters' displays, again several approaches are being taken, such as movement of a single numbered and colored band every tenth dose in the Trudell Medical International top-mount actuation indicator, incremental movement of a single band every dose (105), or multi-ring dose-by-dose numerical counting (106). Both direct numeric and color-coded displays can be acceptable based on the FDA dose counter guidance (97). In addition to mechanical dose counters, several electronic counters have been developed or proposed. Examples include one developed by Kos (107–109), the Aradigm SmartMist™ device, the Meditrack Doser™, the Smartinhaler Tracker™, and Respirics MD Turbo™ counters which are available as add-on devices. These are able to offer greater sophistication than mechanical systems, and some might also be used as dosing regimen calendars or compliance monitoring aids. Electronic systems may, however, require additional validation to satisfy the regulatory authorities, and issues of cost and battery reliability certainly need consideration.

NASAL MDIs

MDIs were once used widely in the treatment of allergic rhinitis, but have been replaced with aqueous pump sprays since the Montreal Protocol (110) did not provide a "medical use" exception for the use of MDIs to treat allergic rhinitis. However, there are several benefits of using MDIs that are leading to the development of new HFA MDIs for treatment of allergic rhinitis. One benefit of MDI systems is the ability to avoid the use of preservatives in the formulation. The design of MDI systems and MDI formulations inherently inhibit microbial growth. This is not true with aqueous pump spray systems. Because of this, most commercially available aqueous pump sprays contain the preservative benzalkonium chloride. Benzalkonium chloride has been shown to adversely affect nasal mucosa (111–113) and prolonged exposure has been shown to induce nasal mucosal swelling (111).

An additional factor that is likely to lead to the re-emergence of nasal MDIs is the fact that the same corticosteroid formulations used in asthma therapies are often therapeutically effective for treating allergic rhinitis. As a result, the development activities to optimize the formulation and container closure system (i.e., the valve and canister) and demonstrate stability for an MDI to treat asthma can be directly leveraged for an MDI to treat allergic rhinitis (or vice versa). For example, QNASL™ (nasal MDI formulation of BDP) leveraged the formulation and container closure development associated with QVAR® and Zetonna™ (nasal MDI formulation of ciclesonide) leveraged Alvesco® development. An additional benefit is the fact that some patients prefer nasal MDI systems over aqueous pump sprays due to the dripping sensation in the nasal cavity and throat after administration of some aqueous pump spray products. Due to these and other considerations, several HFA MDIs have recently been commercialized or are currently in development for treatment of allergic rhinitis.

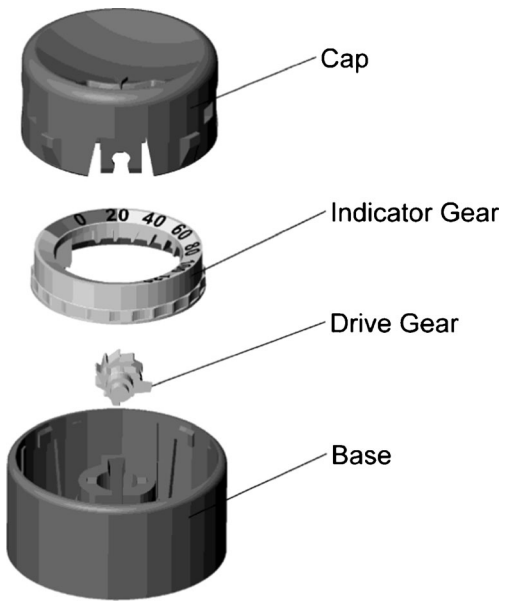

Fig. 9. An exploded view of the four components of a Trudell Medical International top mount actuation indicator. Drawing courtesy of Trudell Medical International

CONCLUSION

More than 50 years after its invention, the MDI remains a mainstay of asthma and COPD therapy worldwide. MDIs are a compact and convenient delivery system that has the advantage of being well understood by patients, physicians, and regulators. The inherent multi-dose nature of MDIs makes them more affordable than most competing inhalation delivery systems. Despite many similarities, MDIs have changed in many ways since the humble starting point in which they were made with glass vials and valves designed for perfume bottles (3). MDI valves have been redesigned to be compatible with HFA propellants, to have reduced extractables and leachables, to enhance dosing uniformity, and to overcome loss of prime during storage. MDI canisters have been developed with surface modifications that greatly reduce drug deposition and drug or canister degradation. MDI actuators have been developed to enhance drug delivery efficiency and provide a more aesthetically pleasing user interface for the patient. Breath-actuated technologies and add-on devices have been developed to further enhance drug delivery efficiency and minimize patient coordination challenges. Dose indicators and dose counters are now utilized to provide patients with information so that they know when to replace their MDI. Furthermore, MDI device technologies are in development and will continue to enhance MDI delivery in the future. Many of the future improvements in MDI technology will increase the ability of MDI systems to meet regulatory specifications, but will be transparent to the patients using the devices. Innovations that enhance the

functionality of MDIs will be balanced by the fact that a key advantage of MDI systems is their low cost per dose. The expansion of the health care market in developing countries and the increased focus on health care costs in many developed countries will ensure that MDIs remain a crucial delivery system for treating lung diseases for many years to come.

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