The pressurized metered dose inhaler: Past, present and future perspectives

The pressurized metered dose inhaler has been widely used for more than 60 years. How has it evolved, and how might it evolve further?

Stephen P. Newman, PhD
Scientific Consultant

Introduction: Fumes, vapors and nebulizers

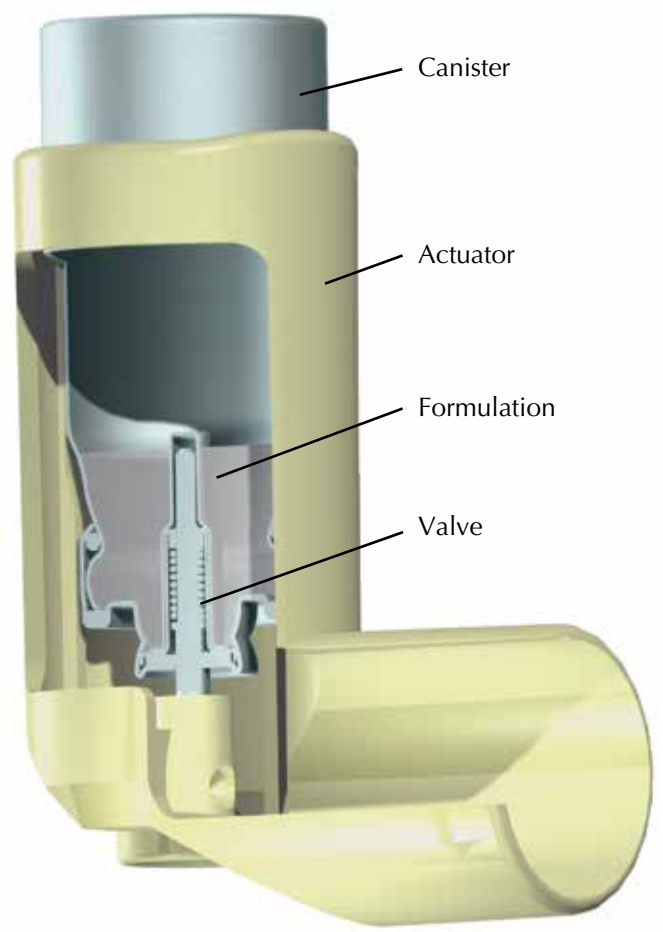
Inhaled drug delivery has a rich history extending over thousands of years,[1] but for much of this time it involved burning plant materials and inhaling the fumes. The development of the first "atomizers" to deliver water droplets at thermal spas in Europe in the 19th century signaled a clear shift away from vapors towards aerosols. From this beginning, a range of inhaler devices has evolved, and continues to evolve today.[2]

There are several driving forces behind this evolution, reflecting the needs (a) to develop convenient and affordable inhalers that patients will use and can use correctly, (b) to deliver an increasingly wide range of drugs by inhalation, and (c) for some drugs, to improve the efficiency of drug delivery and make it less variable. The field is dominated by the maintenance therapy of asthma and chronic obstructive pulmonary disease (COPD), but the pulmonary route is also used to deliver drugs to treat several less common lung diseases, as well as being a portal of entry for drugs required to act systemically.

The use of hand-held, squeeze-bulb nebulizers to deliver inhaled epinephrine for treatment of asthma attacks was first reported in the early 20th century, and this practice became more common as the century progressed. The glass DeVilbiss no. 40 nebulizer (available in the 1930s) and other similar models became well known. But these devices suffered from two important limitations: they were fragile and easily broken, and they delivered a variable dose that depended on the amount of pressure applied. It was the desire of Riker Laboratories in the mid-1950s to provide patients with a more robust and reliable dosage form that led scientists there, including Charles Thiel and Irving Porush, to invent the first pressurized metered dose inhalers (pMDIs) in 1956.[3] The pMDI has recently celebrated its 60th birthday.

Figure 1

Schematic of a typical pMDI. Key components are the canister, actuator, formulation and metering valve. Although the pMDI now looks much the same as it did in 1956, the device has undergone many changes and improvements. Originally published in Bell and Newman, Expert Opin. Drug Deliv. 2007; 4: 215-234; www.tandfonline.com.



The first pMDIs

Technical innovations can be classified as sustaining, disruptive or revolutionary,[4] with most innovations being sustaining. The pMDI was a disruptive innovation when introduced in 1956, because it allowed users to address the challenge of drug delivery to the lungs in a radically new way. The pMDI is a complex device with several key components, including formulation and metering valve (Figure 1). Fortuitously, its development coincided with the recent availability of suitable 50 µL

Table 1

Various key dates in the history of pMDIs.

1956	First pMDIs (Riker): isoproterenol (Medihaler Iso™) and epinephrine (Medihaler Epi™)
1956	Medihaler Nitro™ (Riker) marketed for treatment of angina; withdrawn in 1958
1957	First nasal pMDI (Medihaler Phen™, Riker) marketed
1959	Medihaler Ergotamine™ (Riker) marketed for migraine therapy
1962	First pMDI containing two drugs, isoproterenol and phenylephrine (Medihaler Duo™, Riker)
1968	First albuterol pMDI (Ventolin®, A&H) marketed in Europe
1970	First breath-actuated pMDI (Autohaler®, Riker)
1972	First beclomethasone dipropionate pMDI (Becotide®, A&H) marketed in Europe
1976	First valved holding chamber (Nebuhaler®, Astra) patented
1981	Albuterol pMDIs marketed in US (Ventolin, Glaxo; Proventil®, Schering)
1982	Beclomethasone dipropionate pMDIs in US (Vanceril®, Glaxo; Beclovent®, Schering)
1987	Montreal Protocol requires phase out of CFC propellants
1995	First HFA-134a albuterol pMDI launched in UK (Airomir®, 3M)
1996	First HFA-134a albuterol pMDI launched in US (Proventil, Schering)
2000	Launch of first HFA-134a beclomethasone dipropionate pMDI (Qvar®, 3M)
2001	Ventolin HFA (GSK) launched in US
2003	FDA recommends that all new pMDIs incorporate dose counters
2004	First pMDI with integrated dose counter (Seretide™ Evohaler™, GSK)
2006	First HFA-227ea pMDI containing budesonide and formoterol (Symbicort®, AstraZeneca)
2006	Advair® HFA (GSK) containing fluticasone propionate and salmeterol approved in US
2010	CFC pMDI phase out completed in Europe
2011	CFC pMDI phase out completed in US
2015	Launch of Sirdupla™ (Mylan) as generic version of Seretide Evohaler in Europe
2016	Amendment to Montreal Protocol proposes reduction in use of HFA-134a and HFA-227ea

A&H: Allen and Hanbury, GSK: GlaxoSmithKline

metering valves that were patented by Philip Meshberg.[3] The first pMDI products (Medihaler Epi™ and Medihaler Iso™, containing epinephrine and isoproterenol, respectively, Riker Laboratories) were formulated with the drug in solution in a mixture of two chlorofluorocarbons (CFC-12 and CFC-114), together with ascorbic acid as an antioxidant and ethanol as a co-solvent. By today's standards, the development and approval of the first pMDIs occurred with remarkable speed and the New Drug Application (NDA) dossier was only 13 mm thick. The introduction of these products marked the beginning of the modern era of inhaled drug delivery.[2]

Several other important developments involving both topical and systemic drug delivery followed from the same team at Riker Laboratories (Table 1), including pMDIs delivering drugs to treat angina (Medihaler Nitro™) and migraine (Medihaler Ergotamine™), and the first "combination" inhaler containing two drugs (Medihaler Duo™). The problem of "loss of prime" caused by formulation draining out of the metering chamber during storage was quickly recognized and addressed by adding a retaining cup that surrounded the valve, a feature that is still used today. The earliest pMDIs were formulated with drug dissolved in propellants, but these products tended to have low fine particle doses owing to the presence in the spray of high concentrations of non-volatile excipients. The first suspension pMDI formulations were available from 1957, with oleic acid surfactant being used to minimize particle aggregation.

The pMDI became the most important drug delivery device for treatment of asthma and related conditions, a position which it still holds 60 years later. Selective $beta_2$-agonists including albuterol, and inhaled corticosteroids including beclomethasone dipropionate, were

Table 2

Properties of propellants that have been, or could be, used in pMDIs. Data compiled from multiple sources.

Propellant	BP (°C)	ODP	GWP
CFC-11	22.8	1	4000
CFC-12	-29.8	1	8500
CFC-114	3.6	1	9300
HFA-134a	-26.2	0	1300
HFA-227ea	-17.1	0	3350
HFA-152a	-24.7	0	138
HFO-1234yf	-29.0	0	4
HFO-1234ze	-19.0	0	6

BP: boiling point, ODP: ozone depletion potential relative to CFC-11, GWP: global warming potential relative to CO_2

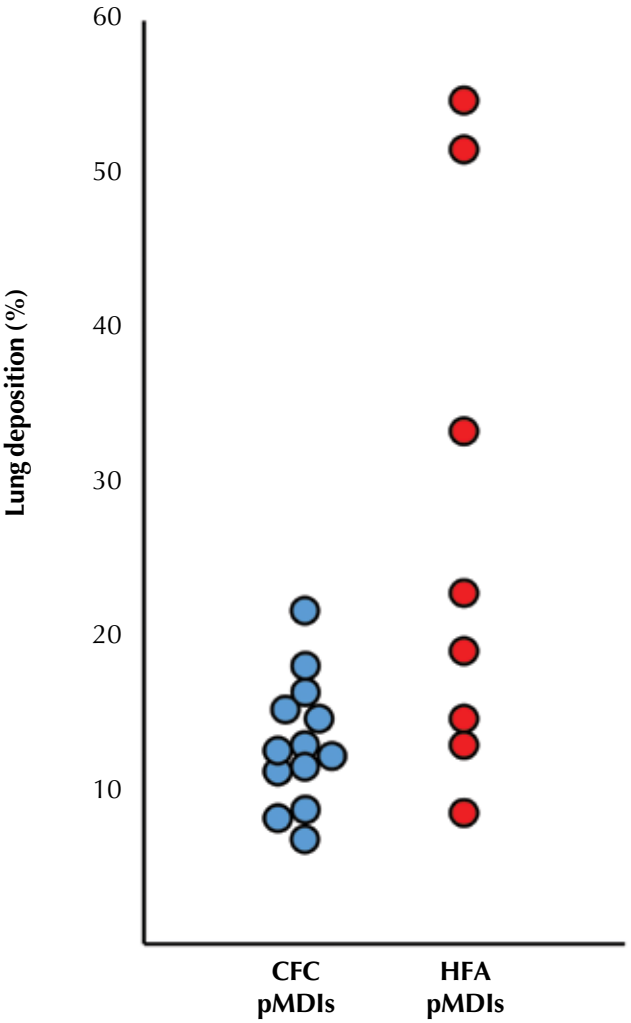
given by pMDI from the 1970s, and were followed over the ensuing decades by products containing long-acting beta-agonists (LABAs), novel inhaled corticosteroids with high receptor binding affinity and low oral bioavailability, and anti-muscarinic agents. Until the mid-1990s, all pMDIs contained two or three CFCs. The highly volatile CFC-12, having a low boiling point (Table 2), was largely responsible for creating the required pressure within the canister, but CFCs 11 and/or 114 were used to modify the vapor pressure and allow handling of the formulation under laboratory conditions. These pMDIs delivered sprays that were all essentially similar in nature, consisting of cold, high-velocity, short-duration plumes, characteristics which usually resulted in no more than 20% of the dose being deposited in the lungs, with most of the dose being deposited in the oropharyngeal airways (Figure 2).[5] However, for use in asthma and COPD maintenance therapy, this low delivery efficiency was not considered a problem because the drugs concerned were inexpensive, readily available and had wide therapeutic windows.

Propellant transition

The prediction in the 1970s that the breakdown of CFCs and consequent release of chlorine radicals would lead to the destruction of ozone in the stratosphere, followed by the discovery in the 1980s of a hole in the ozone layer, was a threat to the continued existence of pMDIs. Yet it also represented an opportunity to improve and modernize these devices via a series of sustaining innovations. Consortia were formed within the industry to share the costs associated with demonstrating the safety of new non-ozone-depleting propellants. For use in pMDIs, propellants are required to be non-toxic, non-flammable (ideally), compatible with formulations and device hardware, have an appropriate boiling point and density, and acceptable taste and odor.[5] From the early 1990s, pMDIs were reformulated

Figure 2

Examples of mean lung deposition (percent ex-valve or ex-actuator dose) from CFC pMDIs (blue) and HFA pMDIs (red), used with correct inhaler technique. Data are drawn from a variety of published gamma scintigraphic studies. Some HFA pMDIs deposit an amount of drug in the lungs similar to that of CFC pMDIs. Yet other HFA pMDIs deposit a markedly higher percentage of dose in the lungs.



with one of two hydrofluoroalkanes (HFA-134a or HFA-227ea), propellants that do not contain chlorine. Essential Use Allowances (EUAs) were issued to permit the continued use of CFCs in pMDIs during the transition process, where such use was considered necessary. Propellant transition has been completed in the US and Europe (Table 1), but an EUA was issued as recently as 2015 for continued use of CFCs in the Chinese market.

In 1995, the first HFA-134a pMDI containing albuterol sulfate reached the market in the UK (Airomir®, 3M) and the same product was marketed in the US the following year (Proventil®, Schering). In 2006, the first HFA-227ea pMDI to receive approval from the FDA was Symbicort® (AstraZeneca), containing budesonide and formoterol fumarate (Table 1).

HFA-134a and HFA-227ea have similar thermodynamic properties to those of CFC-12, but there were

Table 3

Formulations of several combination products containing both a bronchodilator and a corticosteroid suspended in HFA propellants, showing how companies have solved formulation challenges in a variety of ways.

Product	Company	Drugs	Propellant and Excipients
Advair® HFA	GlaxoSmithKline	Salmeterol xinofoate Fluticasone propionate	HFA-134a
Dulera®	Merck	Formoterol fumarate Mometasone furoate	HFA-134a Ethanol Oleic acid
Symbicort® HFA	AstraZeneca	Formoterol fumarate Budesonide	HFA-227ea Polyethelene glycol Polyvinylpyrrolidone
Flutiform®	Mundipharma	Formoterol fumarate Fluticasone propionate	HFA-227ea Ethanol Sodium cromoglycate

no direct replacements for CFCs 11 and 114. Further, the surfactants used in CFC formulations proved to have poor solubility in HFA-134a and HFA-227ea. These issues led to a variety of novel formulation strategies, with the use of ethanol being resumed in some products.[6] This variety of formulation strategies is exemplified in modern combination products formulated as suspensions, containing both a bronchodilator and a corticosteroid. As shown in Table 3, several approaches have been used, including two drugs suspended in HFA-134a alone, use of ethanol to dissolve oleic acid surfactant and addition of novel excipients as suspension stabilizers. Novel particle preparation methods such as spray drying have been used in development of experimental products, none of which has yet been marketed.[7]

It soon became clear that propellant transition would require changes to many other components of the device as well. This included the use of new elastomers in the metering valves, e.g., ethylene-propylene-diene monomer (EPDM), in order that the concentrations of leachables and extractables should be acceptably low, as well as new plastics, e.g. polyoxymethylene (POM). Coatings, often consisting of various fluorocarbon polymers, were added to the insides of canisters to minimize deposition of suspension formulations and to avoid chemical degradation of solution formulations. These changes helped to ensure that stringent regulatory requirements for delivered dose content uniformity (DDCU) should be met.[8]

HFA pMDIs developed in two broad directions, with a result that there is much more variation in the characteristics of HFA pMDIs than there was in CFC pMDIs. These developments produced either (a) sprays with similar properties to those of CFC pMDIs, or (b) sprays that are warmer, slower moving ("softer") and of longer duration, and sometimes of a very small particle size. As a result, some pMDIs containing a glucocorticosteroid in solution can deposit 50% of the ex-actuator dose in the lungs (Figure 2), in addition to giving superior delivery to the most peripheral airways (e.g., Qvar®, 3M; Alvesco®, Nycomed). Improved understanding of the factors that determine the characteristics of pMDI sprays have resulted in the generation of empirical equations allowing the fine particle fraction for solution formulations to be predicted as a function of actuator nozzle diameter, metered volume and HFA-134a content.[9] This is the basis of Modulite® technology (Chiesi) where a pMDI spray can be designed to have required characteristics.

Ease of use and additional technologies

Patient education and training aids

It did not take long after their introduction to recognize that although pMDIs are apparently easy to use, they are difficult to use correctly. Correct inhaler technique consists of actuating the inhaler while breathing in slowly and deeply (e.g., over about 5 seconds for adults), and then holding the breath for up to 10 seconds. The problems of inhaler misuse have been recognized for decades. Yet a recent meta-analysis[10] concluded that inhaler technique for both pMDIs and DPIs has not significantly improved over the last 40 years. Education by healthcare professionals about correct inhaler technique is recognized as vital. Training aids such as the 2Tone Trainer™ (Canday Medical) and the Trainhaler™ (In Check Flo-Tone Trainer, Clement Clarke International) were introduced to teach patients how to coordinate the "press and breathe" maneuver, and to inhale at an appropriate flow rate.[11]

Breath-actuated pMDIs

The first breath-actuated pMDI (Autohaler®, Riker Laboratories), where the inhaler is operated by a spring and not by the patient's thumb, was introduced in 1970 to help patients unable to "press and breathe" simultaneously.[3] But it was rather noisy and bulky, and was not

Table 4

Various potential, future, sustaining innovations in pMDI technology

General
Delivery of a wider range of drugs (not just asthma and COPD therapies)
Delivery of larger doses per shot
Increase in magnitude and reduction in variability of lung deposition
Valves
Designs to minimize or eliminate loss of prime
Delivery of two drugs from separate reservoirs
Surface coatings
Novel elastomers and plastics
Canisters
Mini-cans containing small numbers of doses
Novel surface coatings
Actuators
Novel breath-actuated pMDIs
Spray-velocity-modifying devices
More sophisticated pMDIs containing training and monitoring elements
Formulations
Novel formulation strategies including use of engineered particles
Introduction of novel excipients
Controlled-release technologies
Propellants
Novel propellants with even lower global warming potential

popular with patients. Modern breath-actuated pMDIs (e.g. Autohaler, Teva; Easibreathe®, Ivax) are much quieter and more compact, but they are available in only a few products and are apparently not perceived as cost-effective. Breath-actuated pMDIs may be most appropriate for products where market differentiation is sought,[8] and could become used more widely if a greater range of drugs requiring precise delivery is given by pMDIs in the future,[12] but their success may depend on the introduction of simpler designs.

Add-on devices

Add-on devices (also known as "spacer" devices) have been more successful. These have included the 140 mL AeroChamber® (Trudell Medical International) and the 700 mL Volumatic® (GlaxoSmithKline). Add-on devices enable patients to actuate the pMDI into the device and then inhale after a short delay. They also improve targeting of drug to the lungs, by reducing oropharyngeal deposition of drug and often increasing the lung dose.[13] Problems associated with static charge, that can cause airborne particles to be attracted to the device walls, have been addressed using static-free plastics. The main disadvantage of add-on devices is their size, but they have been particularly valuable for delivering inhaled drugs to the youngest and oldest patients.

Dose counters

Most pMDIs use aluminum canisters, and the patient cannot see the formulation, so that based on observation alone, there is no certain way of telling when the device needs replacing. Floating the inhaler in water has been used to assess whether the inhaler is nearly empty, but was judged to be highly unreliable,[14] as well as having a potentially adverse effect on the functioning of the device. Recognizing this as a safety issue, the FDA recommended, in 2003, that a dose counter should be fitted to all new pMDIs. It was required that a dose counter should provide a clear indication when the pMDI is approaching the end of the labeled number of doses and when it has reached that number, with these indications giving the patient enough time to get a new inhaler when needed.[15] European guidelines also encouraged the fitting of dose counters to new pMDIs, and the potential for dose counters to provide product differentiation has been recognized. GlaxoSmithKline launched Seretide™ Evohaler™ (containing salmeterol and fluticasone propionate) in 2004, which was the first pMDI with a dose counter incorporated into the device. Landmark™ (Aptar Pharma), Aerocount™ (Trudell Medical International) and Integrated Dose by Dose Counter (3M) are three examples of dose counters.

Connected inhalers

Poor adherence to inhaler therapy has long been recognized as a major problem, resulting in both poorly controlled disease and additional health costs.[11] Attempts to quantify adherence via patient records or by weighing inhalers have proved unreliable; patients are known to enter incorrect data on recording forms and even to "dump doses" immediately prior to clinic visits. These problems have been addressed via "connected inhalers," where attachments to pMDIs and other inhaler types are used to monitor inhaler use. They also provide feedback to the patient and healthcare professionals via smartphones, tablets or desktop computers.[16] In addition, these technologies can provide reminders electronically to patients to take their next dose. Smartinhaler™ (Adherium) and the Propeller sensor (Propeller Health) are two examples of these technologies.[17] In addition, a variety of apps are available for download. These have the broad aims of educating patients about correct inhaler technique, monitoring adherence, providing feedback and helping patients live with chronic disease.

Future developments

Possible future sustaining innovations in pMDI technology could see further changes involving valves, canisters, actuators, formulations and propellants (Table 4).

Most pMDI valves pre-meter the next dose immediately following delivery of the previous dose, retaining the next dose in the metering chamber until required. But even with a retaining cup present, this can lead to loss of prime, either because liquid has been shaken out

by the patient or because vapor bubbles have formed during storage. Instructions for use require that a set number of priming shots should be fired to waste before the inhaler is first used or if the inhaler has not been used recently.[18] Fast-fill fast-empty (FFFE) valves (e.g., Easifill™, Bespak; Face Seal™, 3M) and other designs are intended to overcome problems with loss of prime. Other possible novel valves include a model that can deliver two different drugs, with the canister containing two formulations in separate reservoirs.[15] Surface coatings on valve components may be desirable to minimize drug deposition and reduce friction of moving parts. Novel (even cleaner) elastomers for use in pMDIs continue to be developed.

The desire to use pMDIs for purposes beyond their core role in asthma and COPD maintenance therapy could lead to several future developments. In current pMDIs, the practical upper limit to the amount of drug that can be delivered per shot is about 1 mg, but it may be possible to increase this several-fold, while increasing the fine particle dose to > 1 mg, consequently widening the range of drugs for which pMDIs are suitable.[19] At one time, most pMDIs contained 200 doses, but 60 to 120 doses are now more common. It may be desirable to decrease the number of doses even further for applications other than asthma and COPD maintenance therapy, which might require the use of "mini-cans" containing the reduced number of doses.[8] In addition, the delivery of drugs with narrow therapeutic windows by pMDI could result in the development of novel breath-actuated inhalers.[12]

For some products or some markets, pMDIs could become increasingly sophisticated. Tempo™, (a platform developed by Map Pharmaceuticals) combines breath-actuation with manipulation of airflow within the actuator to reduce the spray velocity. The 3M™ Intelligent Control Inhaler combines breath-actuation, inhaled flow rate control, training in inhaler use, adherence monitoring and feedback to healthcare providers.[20] The use of digital technologies, including connected inhalers and smartphone apps, is likely to become more widespread.

Future developments in pMDI formulations could see the introduction of novel excipients and engineered particles such as Pulmosphere® particles (Novartis). An interesting strategy has been used in development of combinations of up to three drugs, involving micronized drug crystals co-suspended with drug-free microparticles.[21] pMDIs that deliver a high percentage of the dose to the lungs may become more common and these could also result in a reduction in the variability of the lung dose. There is continued interest in increasing the duration of action of inhaled drugs via controlled release technologies, and for some treatment indications, these could find their way into pMDIs.

Although HFA-134a and HFA-227ea have reduced global warming potential compared to CFCs (Table 2), concerns have been expressed that the risk from these propellants is still unacceptably high, if targets to reduce the emissions of greenhouse gases are to be met. HFAs are already the subject of regulation in both the EU and US, and a recent amendment to the Montreal Protocol has proposed a reduction of HFA emissions to about 15% of current levels by 2035.[22] The contribution to global warming of HFAs in pMDIs is negligible,[8] and regulation is aimed mainly at the use of HFAs in air conditioning and refrigeration. The implications for pMDIs are currently unclear, but alternative propellants with similar thermodynamic properties and very low global warming potential (e.g., HFA-152a, and the hydrofluoroolefins HFO-1234yf and HFO-1234ze) have been investigated (Table 2). It has been suggested that a HFA-152a pMDI could have a carbon footprint an order of magnitude lower than that of a HFA-134a pMDI.[23] However, the low density and flammability of HFA-152a could be problematic, and the environmental consequences of both the production and degradation of HFOs have been raised as concerns. Whether these or other propellants will prove necessary and desirable, and whether the industry would have the enthusiasm for another transition process, including the need for extensive toxicity testing and the possible need to replace other device components as well, remains to be seen.

Concluding observations

By targeting drug direct to its site of action (for locally acting drugs such as bronchodilators and corticosteroids) or site of absorption (for inhaled insulin (e.g. Afrezza®, Mannkind) or small molecules such as loxapine (Adasuve®, Alexza)), inhaled drug delivery provides important advantages. Although inhaled drug delivery is challenging, its use is increasing widely and it is likely to have a continued role for both topical and systemic applications in the foreseeable future.

The pMDI looks set to continue as a very popular inhaler device. In the early 1990s, the pMDI was often seen as inefficient, somewhat old-fashioned, difficult to use correctly and environmentally unfriendly.[5] Today, it is recognizable as the 1956 device, but it contains many modern enhancements and is viewed as durable, adaptable and cost-effective. The relatively low cost per dose of pMDIs is attractive in both developed and developing countries. This factor, together with the potential for formulations in dry powder inhalers (DPIs) to be adversely affected by humidity, as well as the potential for the DPI lung dose to depend on the patient's inspiratory effort, are reasons why DPIs are unlikely to totally replace pMDIs. The worldwide output of pMDIs was estimated at 750 million in 2016, with a predicted increase of 5% to 8% per annum.[22]

In 2006, when giving a presentation at a major conference, 50 years after the introduction of the first marketed pMDI, I was asked whether I thought the pMDI would still be around to celebrate its 100th birthday. At that time, I was skeptical, perhaps as much as anything

because of the rapid pace of change in society: was it likely in the modern world that a 100-year-old device would still be used in 2056? Now I'm not so sure that my initial reaction was correct and the pMDI looks like a survivor. My current view is that the pMDI will more than likely still be with us in the middle of this century, unless some completely novel, revolutionary technology is invented, perhaps involving drugs or concepts that we cannot imagine at present.

Disclaimer

A variety of companies have been named in this article but the text is not meant to be exhaustive and any exclusions are not intentional.

References

1. Anderson PJ. History of aerosol therapy; liquid nebulization to MDIs and DPIs. Respir. Care 2005; 50: 1139-1150.

2. Stein SW, Thiel CG. The history of therapeutic aerosols: A chronological review. J. Aerosol Med. Pulm. Drug Deliv. 2017; 30: 20-41.

3. Thiel CG. From Susie's question to CFC free: An inventor's perspective on forty years of MDI development and regulation. In: RN Dalby, PR Byron, SJ Farr, (eds): Respiratory Drug Delivery V. Buffalo Grove: Interpharm Press, Buffalo Grove, IL, US; pp 115-123, 1996.

4. Smith IJ, Bell J, Bowman N, Everard M, Stein S, Weers JG. Inhaler devices: What remains to be done? J. Aerosol Med. Pulm. Drug Deliv. 2010; 23 (Supplement 2): S25-S37.

5. Bell J, Newman SP. The rejuvenated pressurised metered dose inhaler. Expert Opin. Drug Deliv. 2007; 4: 215-234.

6. Myrdal PB, Sheth P, Stein SW. Advances in metered dose inhaler technology: Formulation development. AAPS PharmSciTech. 2014; 15: 434-455.

7. Weers JG, Bell J, Chan H-K, Cipolla D, Dunbar C, Hickey AJ, Smith IJ. Pulmonary formulations: What remains to be done? J. Aerosol Med. Pulm. Drug Deliv. 2010; 23 (Supplement 2): S5-S23.

8. Stein S, Fradley G. What is the future of MDIs? In: RN Dalby, PR Byron, J Peart, JD Suman, SJ Farr, PM Young, (eds): Respiratory Drug Delivery 2010. Davis Healthcare International, River Grove, IL, US; pp 373-376, 2010.

9. Lewis DA, Ganderton D, Meakin BJ, Brambilla G. Theory and practice with solution systems. In: RN Dalby, PR Byron, J Peart, JD Suman, SJ Farr, (eds): Respiratory Drug Delivery IX. Davis Healthcare International, River Grove, IL, US; pp 109-115, 2004.

10. Sanchis J, Pedersen S, on behalf of the ADMIT team. Systematic review of errors in inhaler use: Has patient technique improved over time? Chest 2016; 150: 394-406.

11. Newman SP. Improving inhaler technique, adherence to therapy and precision of dosing: Major challenges for pulmonary drug delivery. Expert Opin. Drug Deliv. 2014; 11: 365-378.

12. Byron PR. Platform selection for inhaled drugs: Biological and regulatory merit of different approaches. In: RN Dalby, PR Byron, J Peart, JD Suman, (eds): Respiratory Drug Delivery Europe 2005. Davis Healthcare International, River Grove, IL, US; pp 1-17, 2005.

13. Nikander K, Nicholls C, Denyer J, Pritchard J. The evolution of spacers and valved holding chambers. J. Aerosol Med. Pulm. Drug Deliv. 2014; 27 (Supplement 1): S4-S23.

14. Rubin BK, Durotoye L. How do patients determine that their metered-dose inhaler is empty? Chest 2004; 126: 1134-1137.

15. Stein SW, Sheth P, Hodson PD, Myrdal PB. Advances in metered dose inhaler technology: Hardware development. AAPS PharmSciTech. 2014; 15: 326-337.

16. Kikidis D, Konstantinos V, Tzovaras D, Usmani OS. The digital asthma patient: The history and future of inhaler based health monitoring devices. J. Aerosol Med. Pulm. Drug Deliv. 2016; 29: 219-232.

17. Sutherland G. Connected inhalers making a real impact on respiratory outcomes. OnDrugDelivery 2016; June: 32-35.

18. Fradley G, Hodson D. Optimization of fluid flow in pMDI valves. In: RN Dalby, PR Byron, J Peart, JD Suman, SJ Farr, PM Young, (eds): Respiratory Drug Delivery 2008. Davis Healthcare International, River Grove, IL, US; pp 329-332, 2008.

19. Stein SW, Forsyth BR, Stefely JS, Christensen JD, Alband TD, Jinks PA. Expanding the dosing range of metered dose inhalers through formulation and hardware optimization. In: RN Dalby, PR Byron, J Peart, JD Suman, SJ Farr, (eds): Respiratory Drug Delivery IX. Davis Healthcare International, River Grove, IL, US; pp 125-133, 2004.

20. Slowey A, Stein S. 60 years of the MDI—A history of innovation. In: Drug Delivery to the Lungs 27. The Aerosol Society, Portishead, UK, on-line abstract, 2016.

21. Vehring R, Lechuga-Ballesteros D, Joshi V, Noga B, Dwivedi SK. Cosuspensions of microcrystals and engineered microparticles for uniform and efficient delivery of respiratory therapeutics from pressurized metered dose inhalers. Langmuir 2012; 28: 15015-15023.

22. Noakes T, Corr S. Pressurised metered dose inhaler propellants: Going forward. In: RN Dalby, PR Byron, J Peart, J Suman, PM Young, D Traini, (eds): Respiratory Drug Delivery Europe 2017. Davis Healthcare International, River Grove, IL, US; pp 255-258, 2017.

23. Jeswani H, Azapagi A. Environmental assessment of metered dose inhaler propellant: Potential for a reduced carbon footprint alternative. In: RN Dalby, PR Byron, J Peart, J Suman, PM Young, D Traini, (eds): Respiratory Drug Delivery Europe 2017. Davis Healthcare International, River Grove, IL, US; pp 355-358, 2017.

Stephen P. Newman, PhD is a Scientific Consultant based in Norfolk, UK. steve.newman_1@btinternet.com.