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Key points

- The dictionary definition of innovation is the introduction of new things, ideas or ways of doing something. We show how this definition can be applied to inhaled therapy.
- We take a look at the past to see what drove innovation in inhaler design and how this has led to the current devices.
- We look at the current drivers of innovation in engineering, chemistry and digital technology and predict how this may translate to new devices.
- Can innovation help the healthcare professional manage their patients better?
- What does the patient expect from innovation in their device?

Educational aims

- To understand the importance of inhaled medication in the treatment of lung diseases.
- To understand how innovation has helped advance some of the devices patients use today from basic and inefficient designs.
- To understand the obstacles that prevent patients from receiving optimal treatment from their inhalers.
- To understand how innovation in inhaler design can lead to improved treatment for patients and widen the range of diseases that can be treated *via* the inhaled route.

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Is there room for further innovation in inhaled therapy for airways disease?

Cite as: Biddiscombe MF, Usmani OS. Is there room for further innovation in inhaled therapy for airways disease? *Breathe* 2018; 14: 216–224.

Inhaled medication is the cornerstone in the treatment of patients across a spectrum of respiratory diseases including asthma and chronic obstructive pulmonary disease. The benefits of inhaled therapy have long been recognised but the most important innovations have occurred over the past 60 years, beginning with the invention of the pressurised metered dose inhaler. However, despite over 230 different device and drug combinations currently being available, disease control is far from perfect.

Here we look at how innovation in inhaler design may improve treatments for respiratory diseases and how new formulations may lead to treatments for diseases beyond the lungs. We look at the three main areas where innovation in inhaled therapy is most likely to occur: 1) device engineering and design; 2) chemistry and formulations; and 3) digital technology associated with inhalers. Inhaler design has improved significantly but considerable challenges still remain in order to continually innovate and improve targeted drug delivery to the lungs. Healthcare professionals want see innovations that motivate their patients to achieve their goal of improving their health, through better adherence to treatment. Patients want devices that are easy to use and to see that their efforts are rewarded by improvements in their condition.

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Can innovation in inhaler design help the healthcare professional manage their patients better and what does the patient expect from any innovation in design? http://ow.ly/pp4w30l1oak

Introduction

Inhaled drug delivery is the cornerstone in the management of patients across a spectrum of respiratory diseases and, more recently, the lungs are being used as a portal for drug delivery to the systemic circulation [1]. It is the preferred delivery route for diseases of the lungs because of the high drug concentration that can be achieved locally within the lungs, leading to improved pharmacological effects and reduced risks of systemic side-effects compared to oral and parenteral medications for the lung. The benefits of inhaled therapy have long been recognised and go back thousands of years [2]. However, real innovation in inhaler technology began just over 60 years ago with the invention of the first pressurised metered dose inhaler (pMDI), which quickly gained widespread acceptance because of its portability and convenience of use. Today, over 90% of the world's short-acting reliever therapy is delivered by a pMDI.

Inhaler and drug development has accelerated in the last couple of decades, with enormous

investment from the pharmaceutical industry. Currently, there are over 230 device and drug combinations available for treating respiratory diseases. The critical stimulus for innovation in inhaler design was the signing of the Montreal Protocol in 1987, banning substances that deplete the protective ozone layer in the atmosphere [3], and paving the way for the abolition of environmentally harmful chlorofluorocarbons used as propellants in pMDIs. The switch to hydrofluoroalkane (HFA)-driven pMDIs not only made an important contribution towards addressing the environmental problem, but also led to a significant number of improvements in the characteristics of the aerosols delivered from these second-generation inhalers [4]. However, not all HFA-pMDIs are the same; there are solution and suspension pMDIs [5]. Most solution pMDIs have the ability to generate finer particles at slower delivery speeds, with the implication of enhanced lung deposition and lower oropharyngeal deposition, and better targeting of drug to the small airways [6]. A few suspension pMDIs also have the aerosol plume as a high fine particle fraction, moving slowly and able to achieve high levels of lung deposition and distal lung penetration [7], where the plume is less affected by inertial forces that cause fast-moving large particles to collide with the throat and oropharynx before reaching the deep lungs.

The Montreal Protocol also led to the diversification of inhaler technologies, with a surge in development to achieve designs for more efficient dry powder inhalers (DPIs) and nebuliser systems [8]. Innovation has not been limited to inhaler design [9] or drug formulation development [10], as during this period, important new drugs have been discovered and developed for the treatment of asthma and chronic obstructive pulmonary disease (COPD) [11]. These include new inhaled corticosteroids (ICSs) and long-acting β-agonists (LABAs), and improved anticholinergic drugs. In addition, the synergistic properties of combining LABAs and corticosteroids has been recognised and has led to the rapid growth in combination therapies and, most recently, triple therapy (three drugs in one inhaler) has been licensed for use in patients with COPD [11]. Important new drug products for the treatment of cystic fibrosis, diabetes and a range of neurological disorders have also been developed [12].

The main classes of delivery systems remain pMDIs, DPIs and nebulisers, but they have recently been joined by a new class of delivery systems called soft mist inhalers (SMIs), where technological and formulation innovation has been well received by patients [13]. Nebulisers have undergone significant development and improvement, with vibrating mesh devices improving the dose delivery efficiency compared to jet and ultrasonic devices [14]. Nevertheless, there are still many opportunities for continued innovation and further development in inhalation technology, but there needs to be appropriate incentives for this to take place.

What are the current incentives driving inhaler development and innovation?

Today we have far more efficient delivery systems and many more potent drugs and drug combinations than in the past. However, asthma and other respiratory diseases still remain a huge healthcare problem, with poor control in ~40% of asthma patients, even on optimally controlled therapy [15]. This can partly be explained by two key challenges facing healthcare professionals and caregivers. These are incorrect inhaler use [16] and poor patient adherence to treatment [17]. The former can be addressed by appropriate and consistent training by the healthcare professionals. Poor adherence to preventive treatment in asthma is harder to deal with and can lead to reduced quality of life and increased symptoms as well as increased use of oral steroids, hospitalisation and mortality. Any new inhaler design needs to benefit patients and their treatment rather than being innovative for the sake of it. Besides the traditional application of locally acting treatments for asthma and COPD, there is still an unmet potential for the systemic delivery of drugs, for example insulin, which has been a goal of scientists since as long ago as 1925, was available for a short period between 2005–2007 and is now again available [18].

Here we look at how innovation may improve treatments for diseases such as asthma and COPD, and more recently cystic fibrosis, but new formulations may also lead to openings for new treatments for diseases beyond the lungs. There are potentially three main areas where we can expect to see innovation in inhaled therapy in the future: 1) innovation in device engineering and design; 2) innovation in chemistry and formulations; and 3) innovation in digital technology associated with inhalers.

Innovation in device engineering and design

Following the initial spike in innovation after the introduction of HFA propellants, pMDI design has largely remained static for the last 20 years. Nevertheless, further design and engineering challenges remain. Innovative engineering, including the development of more consistent metering valves, is necessary to ensure consistency in the dose delivered from the inhaler each time a patient uses it, regardless of the severity of their disease, their lung function or any detrimental effect on their ability to inhale. Future improvements might also include further dose counters, improvement in breath-actuated devices, improved control over emitted particle size distributions and specialised devices for paediatric and geriatric patients [19]. There is also likely to be an emphasis on expanding

the range of drugs that can be delivered with pMDIs [19]. One of the biggest improvements to come from the new pMDI formulations has been based on the scientific discovery showing that the ability to deliver fine particles [20] allows aerosols to penetrate deeper into the lungs to treat the small airways in asthma and also in idiopathic pulmonary fibrosis [21, 22]. With diameters <2 mm, the small airways have been recognised as important sites of chronic inflammation and disease with associated abnormalities [23, 24]. Therefore, for effective treatment of the disease it is important to deliver therapy to both small and large airways [25].

Perhaps the biggest innovation in inhaler design in recent times has been the development of the SMI [26]. This new class of delivery system converts an aqueous liquid solution to an inhalable vapour using the energy of a compressed spring. SMIs are multi-dose and can compete with pMDIs and DPIs on portability and convenience of use, with the added advantages that they do not require propellants or the patient's inspiratory effort to generate the aerosol. They generate a slowly moving mist of fine droplets over ~1.5 s, which makes it easy for the patient to inhale. If the patient adheres to the recommended slow deep inhalation manoeuvre, there is the potential to significantly reduce impaction in the upper airways and increase the dose delivered to all parts of the lungs including the small airways. The Respimat device (Boehringer Ingelheim, Ingelheim, Germany) is the only SMI currently available on the market. However, because of their favourable delivery characteristics, it is likely that there will be more SMI-based delivery systems in the future, including digital versions [26].

Currently, there is growing interest in the use of so-called "extrafine" aerosols, with a mass median aerodynamic diameter of <2.1 µm [27], to target the small airways in the management of asthma and COPD [28], where the prevalence of small airways disease is observed to be ~40% in patients with asthma [29] and ~60% in patients with COPD [30]. The DPI NEXThaler (Chiesi, Parma, Italy) was the first DPI on the market capable of delivering a small-particle ICS/LABA drug combination [31]. It is able to deliver extrafine particles using an innovative release and cyclone airflow mechanism to separate the drug and carrier particles. It accomplishes this by the use of an extrafine drug formulation combined with large carrier particles that are efficiently separated from each other within the cyclone chamber during inhalation. Delivery is activated by patient inhalation only when a threshold inspiratory flow of 35 $L \cdot min^{-1}$ is reached. This is the minimum flow to allow de-aggregation of drug within the cyclone. A dose protector prevents the dose from being inhaled at sub-optimal inhalations, allowing the full dose to be delivered at the correct flow rate. The inhaler also incorporates a full dose feedback system to inform the patient of successful delivery.

Interest in the delivery of new and interesting biopharmaceuticals for pulmonary delivery is gaining pace and DPIs may have the greatest potential for this [32]. In order for this expansion to continue, there is an urgent need for the development of efficient high-dose delivery devices. Early DPIs had poor drug delivery performance due to design weaknesses but were only required to deliver low doses of drug for asthma and COPD. These devices have become far more efficient, but the focus of DPI innovation is gradually shifting to platforms exclusively for the delivery of microparticles, nanoparticles, small molecules and biomacromolecules [12]. More efficient dispersion systems and new particle engineering and powder processing are increasingly being applied to achieve improved lung deposition. In general, DPI medication is delivered using devices specifically designed for the formulation used. When designing a new device, the interaction between the formulation and device must be taken into account, since formulation and device development go hand in hand. Islam and Gladki [33] listed nine characteristics of an ideal DPI, although they qualified this by saying that no actual DPI currently available achieves all of these. Nevertheless, considerable research is being conducted to improve DPI performance and the range of therapeutics they can deliver. One of the major concerns with DPIs, because they are breath actuated, is that the patient may not be able to generate a sufficiently high flow rate to overcome the intrinsic resistance of the device, leading to poor drug extraction and inhalation and sub-optimal therapeutic effect. This concern is being addressed and there are a number of low-resistance devices available [34], as well as so-called third-generation "active" power-assisted devices, which incorporate battery-driven impellers and vibrating piezo-electric crystals to disperse drug from the formulation, reducing the need for the patient to generate a high inspiratory flow rate [4].

Nebulisers are also likely to see further innovation. The dosing reliability of nebulisers has become far more accurate, with jet (pneumatic) and ultrasonic nebulisers giving way to portable vibrating mesh devices enhanced by the integration of software control. Indeed, intelligent nebulisers have been used in clinical trials to treat patients with asthma [35], where they pulse aerosols in greater amounts to the lungs with less waste and with deep lung delivery, and also in systemic delivery to treat patients with pulmonary hypertension [36].

Innovation in device chemistry and formulation

It has been more than 50 years since the introduction of the first DPI. Even so, first-generation devices that use capsules to store and deliver the drug are still widely used with new formulations, despite multiple-dose and multi-unit devices being available. Currently, there is an abundance of developments and diversity of applications for pulmonary

drug delivery as dry powders and formulation developments outnumber those of devices [37]. Many new areas of interest for DPIs are being explored with the use of new techniques such as computational fluid dynamics and other emerging particle engineering technologies. This impetus is likely to result in a new generation of inhaler devices and formulations, which will allow new therapies based on inhaled medicines to be introduced [38].

The use of nanoparticles in pulmonary drug delivery, as in other forms of medicine, is gaining momentum. There are many benefits from using nanoparticles, particularly for drugs with poor solubility and those for systemic delivery [39]. Their large surface area relative to their mass allows rapid drug release and shorter time to reach higher drug concentration at the site of absorption and they are less affected by mucociliary and phagocytic clearance. Their use in inhaled medicine, while relatively new, is likely to increase in the future as more sophisticated methods of formulation, encapsulation and delivery are developed.

With the exception of the Turbuhaler (AstraZeneca, Cambridge, UK), DPI formulations for asthma and COPD have traditionally comprised low doses of micronised drug mixed with a carrier of larger excipient particles such as lactose, which adds bulk to the formulation, improving its flow properties and allowing reproducible capsule or blister filling. It enables the formulation to overcome the cohesive forces of small, micronised pharmaceutical particles, which cause them to stick together or to other surfaces they encounter, leading to poor aerosolisation and delivery performances [21]. Newer applications of powder delivery including high doses of antibiotics to the lungs require carrier-free formulations [40]. This has required new DPI formulations and mechanisms of drug de-agglomeration and dispersion. Advanced particle engineering techniques have been developed and significant effort has been put in to understand the mechanics that control powder dispersion and particle interaction during inhalation [38]. These developments have given rise to a number of carrier-free DPI powder formulations, including soft aggregates of micronised particles called spheroids, coated particles of lipids or amino acids using spray drying methods, Technosphere powder technology (MannKind Corporation, Westlake Village, CA, USA) developed for the delivery of insulin, liposome-based particulate systems and porous particle technologies.

One particle engineering technology, which is currently undergoing development by Prosonix Ltd (Oxford, UK), recently acquired by Circassia Pharmaceuticals plc (Oxford, UK), is the UMAX (Ultrasound Mediated Amorphous to Crystalline transition) process. This has been described as an alternative to micronisation for producing inhalable drug products such as corticosteroids, β-agonists and anticholinergics [41]. The manufacturer states that inhalable UMAX formulations show comparable or superior *in vitro* performance compared to conventional micronised drugs, which they predict will lead to improved clinical performance and patient compliance irrespective of the delivery device.

Technosphere technology is a novel system for the delivery of insulin to the systemic circulation *via* the lungs (Afrezza; MannKind Corporation). The primary component is a new excipient, fumaryl diketopiperazine, in the form of a spherical, crystalline particle with a large surface area that forms a particle matrix [42]. The insulin can be adsorbed on this large surface area to make an inhalation powder. Technosphere particles carry the drug to the lungs following inhalation and rapidly dissolve due to their high solubility at pH ≥6. Absorption begins almost immediately after inhalation and peak concentration in the circulation is achieved within minutes. The carrier particles are small enough to be inhaled, which has the advantage that drug and carrier do not need to be separated before inhalation.

Using porous particles for the delivery of inhaled therapy is another promising area of particle engineering that is likely to be developed further. Large porous particle (LPP) technology was first described more than 20 years ago, but has recently gained in popularity [43, 44]. LPPs are characterised by particles of low mass density (<0.1 g·cm^{-3}) but large physical size (5–30 µm) and are useful for both local and systemic applications. They achieve deep lung penetration, despite their large physical size, by virtue of their low mass density giving them a small aerodynamic diameter, d_{aer}, and high fine particle fraction (≤4.7 µm). Large particles with high porosity can have the same d_{aer} as smaller nonporous particles because the parameter is related to the physical diameter d and mass density ρ by the formula $d_{aer} = d\sqrt{\rho}$. The large physical size aids dispersion and aerosolisation of the powder from the device without the need for a separate carrier. LPPs are especially attractive for systemic inhalation therapies, as their high delivery efficiency and sustained drug release properties allow increased systemic bioavailability. LPPs are commonly produced by spray drying or spray freeze-drying technology [44] and the rapid expansion of supercritical fluids [45].

Another useful feature of LPPs is that they are able to carry a payload of much finer therapeutic particles, "Trojan" style, deep into the lungs where, following dissolution of the carrier, they have the potential for avoidance of alveolar macrophage clearance, enabling sustained drug release throughout the lumen of the lungs. Tsapis *et al.* [46] demonstrated the concept of delivering "hybrid" LPPs containing nanoparticles deep into the lungs. They spray dried solutions of polymeric and nonpolymeric nanoparticles into thin-walled macroscale structures that dissolve in the lungs to release the nanoparticles at the site of delivery. This is a useful characteristic that can prolong the residence of an administered drug in the airways. The

advantage of delivering fine particles encapsulated within LPPs is that the large particles are able to improve the flow properties of the formulation by reducing the number of contact surfaces between adjacent particles. This significantly reduces the aggregation problems normally associated with extremely small particles, which make their use in large doses highly problematic. Tsapis *et al.* [46] described the mechanism as a robust drug delivery system combining the advantages of nanoparticles with the delivery convenience of LPPs. Other groups have since used the concept to deliver nanoparticles to the lungs [47].

PulmoSpheres (Inhale Therapeutic Systems Inc., San Carlos, CA, USA), produced by spray drying, use a proprietary porous particle technology similar to LPPs but with smaller particle sizes (<5 µm). Nevertheless, they possess the same flowability and aerosolisation advantages of LPPs. The technology has been used in the TOBI Podhaler device (Novartis Pharmaceuticals, Basel, Switzerland), which is used for delivering tobramycin for the treatment of infections caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis. Indeed, antimicrobial therapy is one area that has benefitted from extensive recent research and development in inhaled drug delivery to the lungs [48]. It offers the opportunity to achieve high doses of antibiotics directly at the site of infection, without requiring potentially toxic high systemic concentrations, reducing the number of cellular barriers that must be negotiated by the molecule before reaching the bacterial infection. Lung concentrations up to 30 times higher than those measured following intravenous administration can be achieved by inhalation [49]. Besides tobramycin, formulations of colistin, aztreonam and levofloxacin have been approved for the treatment of lung infections in cystic fibrosis, and several other classes are in development [48].

Innovation in digital technology in inhaler devices

Digital technology is advancing rapidly and is now taken for granted in many areas of life that were previously untouched by it. Technology, using mobile phones, is becoming an increasingly popular and easy way for people to monitor their health. A review in 2012 revealed that there were over 100 English language mobile phone applications related to asthma, including 47 tools for the management of asthma [50]. Home monitoring applications can be either an interactive mobile telephone system (mHealth) or based on the Internet. These are promising tools for supporting the self-management of asthma and may help to increase patient adherence. One of the most important applications of digital technology for inhaled delivery systems is electronic monitoring devices for inhalers. Their use is growing rapidly because of their ability to provide detailed and objective data on patient adherence to treatment in order to aid clinical decision making. Patient self-reporting is often unreliable and may over-estimate adherence. Remote monitoring has the potential to allow physicians to monitor patients more reliably and reduce hospital visits. Accurate adherence data could allow clinicians to make better informed care decisions by eliminating sub-optimal adherence as the cause of poor treatment response, thus avoiding unnecessary dose escalations or add-on therapies. One of the biggest obstacles to uptake of the technology has been price. However, prices are falling as the technology becomes more commonplace [51]. As digital remote monitoring becomes an established element of healthcare, its use is likely to increase rapidly [52]. Morrissey [53] described a five-step process for remote monitoring: 1) the device is activated for passive data collection by the caregiver or patient, then the device collects and packages the data ready for transmission; 2) the data are transmitted *via* the Internet, telephone or other electronic method, and received by the appropriate caregiver; 3) the data are reviewed either by an algorithm or a clinician and the information is tabulated, with indicator thresholds of normal and abnormal results embedded in the process to alert the care team if an acute event occurs; 4) an alert is sent to the patient and designated responders who can provide assistance to the patient; 5) treatment is adjusted where necessary and the clinician teaches the patient, caregiver and family about how to avoid similar incidents.

The use of "intelligent" delivery systems is not new. Inhaler monitoring devices were first introduced at the beginning of the 1980s and have been developing ever since for the assessment of medication adherence [54]. A recent review article identified a number of studies that introduced electronic monitoring devices designed either as novel inhalers or inhaler add-ons [54]. These included the Turbuhaler Inhalation Computer, Electronic Diskhaler and Diskus Adherence Logger, all of which are attempts to objectively monitor the use of devices and record the date and time of every valid inhalation. The SmartMist, which introduced sensing capabilities allowing the assessment of inhalation technique in addition to adherence, has been described as an important evolutionary step in smart inhaler design, which also included an innovative mechanism for the automated actuation of MDIs [54].

With increasing integration of microprocessors into inhaler devices, we are likely to see an expanding role for intelligent delivery systems that are able to analyse a patient's breathing patterns to allow more precise control of the drug dose delivered to the lungs [55]. These devices are also able to target specific areas of the lung and minimise drug waste [56]. So-called "intelligent" nebulisers are one such application. The AKITA system is a stand-alone control unit that operates with an electronic SmartCard to coordinate delivery with the patient's breathing pattern. The system works with both jet

Self-evaluation questions

1. In which year was the first pMDI introduced?
   a) 1971
   b) 1996
   c) 1956
   d) 2000
2. What is the main asthma management challenge facing healthcare professionals?
   a) Rising cost of asthma treatment
   b) Poor patient adherence to treatment
   c) Lack of new treatments available
   d) Poor inhaler design
3. What is the main advantage of small particle aerosols?
   a) Their small size allows them to target the small airways better
   b) The drug concentration is higher
   c) The cohesive forces that cause the particles to stick together are lower
   d) Patients don't need to inhale so hard to get the correct dose
4. What is the main advantage of digital technology in inhaled medication?
   a) Patients can get instant feedback of how their asthma is responding to treatment
   b) Inhalers can be made more efficient
   c) Patients know that their inhalers can use the latest technology
   d) It is a useful tool for the self-management of asthma and patients can be remotely monitored by doctors and caregivers

nebulisers (AKITA JET; Vectura GmbH, Gauting, Germany) and the newer mesh nebulisers (AKITA APIXNEB and AKITA2 APIXNEB; PARI Pharma GmbH, Gräfelfing, Germany). A similar system is the I-neb adaptive aerosol delivery system (Philips Respironics, Murrysville, PA, USA). It is a vibrating mesh nebuliser that only delivers aerosol during inhalation [57].

MyAirCoach is an initiative funded by the European Union that is working towards developing a system that helps people with asthma to manage their condition. At present, it is running a trial to assess its usability in patients with asthma. This system promises to be more sophisticated than currently available self-management tools and will involve the combination of a "smart" inhaler and an application for the patient's smart phone or tablet. A smart inhaler contains a number of sensors that will record how well people are taking their medication. It aims to detect small changes in their asthma that they may not even notice. Environmental information will also be recorded, allowing potential triggers to be logged. It is likely that digital technology will play a big role in the next period of inhaler development, allowing improved patient communication and self-management as well as the monitoring of adherence to treatment [54].

Conclusions

Today's inhalers are the result of decades of research, design and innovative engineering and have improved the quality of life of hundreds of millions of people worldwide over this time. Considerable challenges still remain to be overcome in order to continually innovate and improve targeted inhaled drug delivery to the lungs. Forbes *et al.* [58] suggested "open innovation" as a way forward. This would require more collaborative research within the pharmaceutical industry and between industry and academia to increase the future chances of success. This may reduce the pathways to developing new medicines and allow the sharing of costs at a time when development costs are rising. The importance of industry collaborations with academics working on cutting-edge science cannot be underestimated and may lead to the new mechanisms and scientific insights and approaches that will be required to overcome the challenges ahead.

From the healthcare professional's perspective, patient adherence is the biggest obstacle to efficient inhaled therapy. Top of their list would be to see innovation that leads to improved adherence and simpler clinical care. They would like to understand the many reasons for non-adherence in their patients and see innovative approaches that motivate them to engage in self-care. This may involve care models that support shared decision making and involve patient-centred communication around technology that decrease refusals and increase patient satisfaction [59].

Patients may see things differently and might be suspicious of technology that monitors the use of their inhaler. They may see it as a means of punishing rather than empowering them [59]. Innovation should therefore support the process of self-care and not just measure the outcome. It should lead to increased engagement between the user and the healthcare team and be developed with the support of patients themselves. Innovation should motivate patients to achieve the goals of improving their health in the same way that the new generation of health-centred watches and mobile phone applications leads to increased physical activity as owners are driven to improve their daily step counts. Patients would agree with their health carers that any new innovation should lead to an improvement in their condition and not just add to the burden of duties that must be carried out in order to manage their condition.

Conflict of interest

M.F. Biddiscombe reports grants from Boehringer Ingelheim, GlaxoSmithKline and Chiesi, outside the submitted work. O.S. Usmani reports personal fees for consultancy from AstraZeneca, Boehringer

Ingelheim, Chiesi, GlaxoSmithKline, NAPP, Mundipharma, Sandoz, Cipla, Takeda, Zentiva and Trudell Medical; grants/grants pending from AstraZeneca, Boehringer Ingelheim, Chiesi and Edmond Pharma; and payment for lectures, including service on speakers' bureaus, from Boehringer Ingelheim, Chiesi, Cipla, NAPP, Mundipharma, Sandoz and Aerocrine, all outside the submitted work.

References

1. Usmani OS. New developments in inhaled drugs: within and beyond the lungs. *Respiration* 2014; 88: 1–2.
2. Stein SW, Thiel CG. The history of therapeutic aerosols: a chronological review. *J Aerosol Med Pulm Drug Deliv* 2017; 30: 20–41.
3. Ozone Secretariat. The Montreal Protocol on Substances that Deplete the Ozone Layer. 1987. Available from: http://ozone.unep.org/montreal-protocol-substances-deplete-ozone-layer/32506
4. Lavorini F, Fontana GA, Usmani OS. New inhaler devices – the good, the bad and the ugly. *Respiration* 2014; 88: 3–15.
5. Stein SW, Sheth P, Hodson PD, *et al*. Advances in metered dose inhaler technology: hardware development. *AAPS PharmSciTech* 2014; 15: 326–338.
6. Usmani OS. Small-airway disease in asthma: pharmacological considerations. *Curr Opin Pulm Med* 2015; 21: 55–67.
7. Johal B, Murphy S, Tuohy J, *et al*. Plume characteristics of two HFA-driven inhaled corticosteroid/long-acting β_2-agonist combination pressurized metered-dose inhalers. *Adv Ther* 2015; 32: 567–579.
8. Biddiscombe MF, Usmani OS. Inhaler characteristics in asthma. *EU Respir Pulm Dis* 2017; 3: 32–37.
9. Bonini M, Usmani OS. The importance of inhaler devices in the treatment of COPD. *COPD Res Pract* 2015; 1: 9.
10. Ferguson GT, Hickey AJ, Dwivedi S. Co-suspension delivery technology in pressurized metered-dose inhalers for multi-drug dosing in the treatment of respiratory diseases. *Respir Med* 2018; 134: 16–23.
11. Gross NJ, Barnes PJ. New therapies for asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017; 195: 159–166.
12. Hickey AJ. Back to the future: inhaled drug products. *J Pharm Sci* 2013; 102: 1165–1172.
13. Dekhuijzen PN, Lavorini F, Usmani OS. Patients' perspectives and preferences in the choice of inhalers: the case for Respimat® or HandiHaler®. *Patient Prefer Adherence* 2016; 10: 1561–1572.
14. Ehrmann S. Vibrating mesh nebulisers – can greater drug delivery to the airways and lungs improve respiratory outcomes? *Eur Respir Pulmon Dis* 2018; 4: in press.
15. Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *NPJ Prim Care Respir Med* 2014; 24: 14009.
16. Usmani OS, Lavorini F, Marshall J, *et al*. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. *Respir Res* 2018; 19: 10.
17. Dekhuijzen R, Lavorini F, Usmani OS, *et al*. Addressing the impact and unmet needs of nonadherence in asthma and chronic obstructive pulmonary disease: where do we go from here? *J Allergy Clin Immunol Pract* 2018; 6: 785–793.
18. Bell DSH. Finally, after 56 years of type 1 diabetes: a regimen that works. *Postgrad Med* 2018; 130: 409–410.
19. Smith IJ, Bell J, Bowman N, *et al*. Inhaler devices: what remains to be done? *J Aerosol Med Pulm Drug Deliv* 2010; 23: Suppl. 2, S25–S37.
20. Biddiscombe MF, Usmani OS, Barnes PJ. A system for the production and delivery of monodisperse salbutamol aerosols to the lungs. *Int J Pharm* 2003; 254: 243–253.
21. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of β_2-agonist particle size. *Am J Respir Crit Care Med* 2005; 172: 1497–1504.
22. Usmani OS, Biddiscombe MF, Yang S, *et al*. The topical study of inhaled drug (salbutamol) delivery in idiopathic pulmonary fibrosis. *Respir Res* 2018; 19: 25.
23. Usmani OS. Small airways dysfunction in asthma: evaluation and management to improve asthma control. *Allergy Asthma Immunol Res* 2014; 6: 376–388.
24. Bonini M, Usmani OS. The role of the small airways in the pathophysiology of asthma and chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2015; 9: 281–293.
25. Usmani OS. Treating the small airways. *Respiration* 2012; 84: 441–453.
26. Fink JB, Colice GL, Hodder R. Inhaler devices for patients with COPD. *COPD* 2013; 10: 523–535.
27. Hillyer EV, Price DB, Chrystyn H, *et al*. Harmonizing the nomenclature for therapeutic aerosol particle size: a proposal. *J Aerosol Med Pulm Drug Deliv* 2018; 31: 111–113.
28. Lavorini F, Pedersen S, Usmani OS. Dilemmas, confusion, and misconceptions related to small airways directed therapy. *Chest* 2017; 151: 1345–1355.
29. Usmani OS, Singh D, Spinola M, *et al*. The prevalence of small airways disease in adult asthma: a systematic literature review. *Respir Med* 2016; 116: 19–27.
30. Crisafulli E, Pisi R, Aiello M, *et al*. Prevalence of small-airway dysfunction among COPD patients with different GOLD stages and its role in the impact of disease. *Respiration* 2017; 93: 32–41.
31. Corradi M, Chrystyn H, Cosio BG, *et al*. NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclometasone and formoterol to treat large and small airways in asthma. *Expert Opin Drug Deliv* 2014; 11: 1497–1506.
32. Frijlink HW, De Boer AH. Dry powder inhalers for pulmonary drug delivery. *Expert Opin Drug Deliv* 2004; 1: 67–86.
33. Islam N, Gladki E. Dry powder inhalers (DPIs) – a review of device reliability and innovation. *Int J Pharm* 2008; 360: 1–11.
34. Colthorpe P, Voshaar T, Kieckbusch T, *et al*. Delivery characteristics of a low-resistance dry-powder inhaler used to deliver the long-acting muscarinic antagonist glycopyrronium. *J Drug Assess* 2013; 2: 11–16.
35. Vogelmeier C, Kardos P, Hofmann T, *et al*. Nebulised budesonide using a novel device in patients with oral steroid-dependent asthma. *Eur Respir J* 2015; 45: 1273–1282.
36. Hill NS, Preston IR, Roberts KE. Inhaled therapies for pulmonary hypertension. *Respir Care* 2015; 60: 794–805.
37. de Boer AH, Hagedoorn P, Hoppentocht M, *et al*. Dry powder inhalation: past, present and future. *Expert Opin Drug Deliv* 2017; 14: 499–512.
38. Hoppentocht M, Hagedoorn P, Frijlink HW, *et al*. Technological and practical challenges of dry powder inhalers and formulations. *Adv Drug Deliv Rev* 2014; 75: 18–31.
39. Zhang J, Wu L, Chan HK, *et al*. Formation, characterization, and fate of inhaled drug nanoparticles. *Adv Drug Deliv Rev* 2011; 63: 441–455.
40. Healy AM, Amaro MI, Paluch KJ, *et al*. Dry powders for oral inhalation free of lactose carrier particles. *Adv Drug Deliv Rev* 2014; 75: 32–52.
41. Ruecroft G, Parikh D, Jones C. Delivering improved respiratory medicines with industrial ultrasonic particle engineering. *J Aerosol Med Pulm Drug Deliv* 2011; 24: A63.
42. Leone-Bay A, Baughman R, Smutney C, *et al*. Innovation in drug delivery by inhalation. *ONdrugDELIVERY* 2010. Available from: http://ondrugdelivery.com/publications/OINDP%20November%202010/Mannkind.pdf.
43. Edwards DA, Hanes J, Caponetti G, *et al*. Large porous particles for pulmonary drug delivery. *Science* 1997; 276: 1868–1871.
44. Ogienko AG, Bogdanova EG, Trofimov NA, *et al*. Large porous particles for respiratory drug delivery. Glycine-based formulations. *Eur J Pharm Sci* 2017; 110: 148–156.
45. Dhanda DS, Tyagi P, Mirvish SS, *et al*. Supercritical fluid technology based large porous celecoxib-PLGA microparticles do not induce pulmonary fibrosis and sustain drug delivery

Suggested answers

1. c.
2. b.
3. a.
4. d.

and efficacy for several weeks following a single dose. *J Control Release* 2013; 168: 239–250.
46. Tsapis N, Bennett D, Jackson B, *et al.* Trojan particles: large porous carriers of nanoparticles for drug delivery. *Proc Natl Acad Sci USA* 2002; 99: 12001–12005.
47. McBride AA, Price DN, Lamoureux LR, *et al.* Preparation and characterization of novel magnetic nano-in-microparticles for site-specific pulmonary drug delivery. *Mol Pharm* 2013; 10: 3574–3581.
48. Woods A, Rahman KM. Antimicrobial molecules in the lung: formulation challenges and future directions for innovation. *Future Med Chem* 2018; 10: 575–604.
49. Goldstein I, Wallet F, Nicolas-Robin A, *et al.* Lung deposition and efficiency of nebulized amikacin during *Escherichia coli* pneumonia in ventilated piglets. *Am J Respir Crit Care Med* 2002; 166: 1375–1381.
50. Huckvale K, Car M, Morrison C, *et al.* Apps for asthma self-management: a systematic assessment of content and tools. *BMC Med* 2012; 10: 144.
51. Chan AH, Harrison J, Black PN, *et al.* Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians. *J Allergy Clin Immunol Pract* 2015; 3: 335–349.
52. Simpson AJ, Honkoop PJ, Kennington E, *et al.* Perspectives of patients and healthcare professionals on mHealth for asthma self-management. *Eur Respir J* 2017; 49: 1601966.
53. Morrissey J. Remote patient monitoring: how mobile devices will curb chronic conditions. *Med Econ* 2014. www.medicaleconomics.com/health-care-information-technology/remote-patient-monitoring-how-mobile-devices-will-curb-chronic-conditions
54. Kikidis D, Konstantinos V, Tzovaras D, *et al.* The digital asthma patient: the history and future of inhaler based health monitoring devices. *J Aerosol Med Pulm Drug Deliv* 2016; 29: 219–232.
55. Zhou QT, Tang P, Leung SS, *et al.* Emerging inhalation aerosol devices and strategies: where are we headed? *Adv Drug Deliv Rev* 2014; 75: 3–17.
56. Darquenne C, Fleming JS, Katz I, *et al.* Bridging the gap between science and clinical efficacy: physiology, imaging, and modeling of aerosols in the lung. *J Aerosol Med Pulm Drug Deliv* 2016; 29: 107–126.
57. Geller DE, Kesser KC. The I-neb Adaptive Aerosol Delivery System enhances delivery of α_1-antitrypsin with controlled inhalation. *J Aerosol Med Pulm Drug Deliv* 2010; 23: Suppl. 1, S55–S59.
58. Forbes B, Asgharian B, Dailey LA, *et al.* Challenges in inhaled product development and opportunities for open innovation. *Adv Drug Deliv Rev* 2011; 63: 69–87.
59. George M. User perspectives on innovation in inhalers. International Society of Aerosols in Medicine (ISAM)/International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) Joint Workshop: New Frontiers in Inhalation Technology. ISAM congress 2017, Santa Fe. https://ipacrs.org/assets/uploads/outputs/MaureenGeorge_SantaFeJune2017.pdf