100 Years of Drug Delivery to the Lungs

Federico Lavorini, Francesca Buttini, and Omar S. Usmani

Contents

Abstract

Inhalation therapy is one of the oldest approaches to the therapy of diseases of the respiratory tract. It is well recognised today that the most effective and safe means of treating the lungs is to deliver drugs directly to the airways. Surprisingly, the delivery of therapeutic aerosols has a rich history dating back more than 2,000 years to Ayurvedic medicine in India, but in many respects, the introduction of the first pressurised metered-dose inhaler (pMDI) in 1956 marked the beginning of the modern pharmaceutical aerosol industry. The pMDI was

F. Lavorini (✉)
Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
e-mail: federico.lavorini@unifi.it

F. Buttini
Food and Drug Department, University of Parma, Parma, Italy

O. S. Usmani
National Heart and Lung Institute, Imperial College London and Royal Brompton Hospital, London, UK

J. E. Barrett et al. (eds.), *Concepts and Principles of Pharmacology*,
Handbook of Experimental Pharmacology 260, https://doi.org/10.1007/164_2019_335

the first truly portable and convenient inhaler that effectively delivered drug to the lung and quickly gained widespread acceptance. Since 1956, the pharmaceutical aerosol industry has experienced dramatic growth. The signing of the Montreal Protocol in 1987 to reduce the use of CFCs as propellants for aerosols led to a surge in innovation that resulted in the diversification of inhaler technologies with significantly enhanced delivery efficiency, including modern pMDIs, dry powder inhalers and nebuliser systems. There is also great interest in tailoring particle size to deliver drugs to treat specific areas of the respiratory tract. One challenge that has been present since antiquity still exists, however, and that is ensuring that the patient has access to the medication and understands how to use it effectively. In this article, we will provide a summary of therapeutic aerosol delivery systems from ancient times to the present along with a look to the future.

Keywords
Aerosol · Dry powder inhalers · Inhalation medicines · Metered dose inhaler · Nebulisers

1 The History of Therapeutic Aerosols: From the Ancient Time to Present

The delivery of therapeutic vapours and aerosols through inhalation has been used for thousands of years in various cultures. Although the term "aerosol" was coined at the beginning of the twentieth century, the use of therapeutic aerosols dates back at least 4,000 years (Stein and Thiel 2017). The origins of inhalation therapy for asthma and other lung diseases may have arisen in the traditional therapies of Ayurvedic medicine in India around 2000 BC. The compounds smoked for medicinal purposes included herbal preparations, most notably *Datura* species, which contain potent alkaloids with anticholinergic properties (Stein and Thiel 2017). An Egyptian papyrus dating back to around 1500 BC describes patients breathing the vapour of the black henbane plant, a herb with anticholinergic bronchodilating properties, after being thrown onto a hot brick (Sanders 2007). One of the earliest inhaler devices is attributed to Hippocrates that consisted of a pot with a reed through which the vapour could be inhaled. By the first century AD, native cultures from Central and South America fashioned pipes to smoke tobacco and other plants. It is believed that these cultures had identified the smoking of plants with anticholinergic properties such as *Datura*, henbane and belladonna as therapeutic remedies to treat respiratory conditions (Sanders 2007). Variations on the Hippocrates's pot-and-reed design were used in the late of the eighteenth and early nineteenth century. The modern era of aerosol therapy began in 1778 with the English physician John Mudge who coined in his book *A Radical and Expeditious Cure for a Recent Catarrhous Cough* the term "inhaler" and described his device for inhaling opium vapour for the treatment of cough (Mudge 1778). The Mudge inhaler, the first known example of a marketed inhaler device, consisted of a pewter tankard with a mouthpiece covering the top and an air passage drilled through

the handle, so that, by inhaling through the mouthpiece, a patient can draw air through the liquid at the bottom of the vessel (Stein and Thiel 2017). Several models of ceramic inhalers followed the design of the Mudge inhaler and were popular from the nineteenth century onward. The last half of the nineteenth century saw unprecedented innovation in the technologies developed by the pharmaceutical for aerosol delivery. The first pressurised inhaler was the Sales-Giron's Pulverisateur in 1858. Many other nebulisers, asthma cigarettes containing stramonium and powders, were introduced in the late nineteenth and early twentieth century, and attempts were made to administer a number of medications by aerosol (Stein and Thiel 2017). The Aerohalor, developed by Abbott Laboratories and launched in 1948 for inhaled penicillin G powder, was the first truly commercially successful dry power inhaler (DPI). The device utilised a steel ball that moved when the patient inhaled and tapped the cartridge that contained the drug to aerosolise the powder. The device was a breakthrough in terms of commercial viability of a DPI device in spite of the fact that it was relatively inefficient in terms of dispersing the powder into a respirable aerosol.

Just over 60 years ago, Charlie Thiel and colleagues at Riker Laboratories (now 3M Pharmaceuticals, St Paul, Minnesota, USA) invented the pressurised metered-dose inhaler (pMDI) after Susie Maison, the daughter of a Riker Vice-President asked, "Why can't you make my asthma medicine like mother's hair spray?". The pMDI was a revolution and, with minor modifications, is still the most popular form of aerosol delivery (Roche and Dekhuijzen 2016). There have been remarkable advances in the technology of devices and formulations for inhaled drugs in the past 50 years since the development of the first pMDI. Jet, ultrasonic and vibrating mesh nebulisers have advanced with devices that are breath-actuated or breath-enhanced. Some milestones in the development of inhaler therapy are shown in Fig. 1.

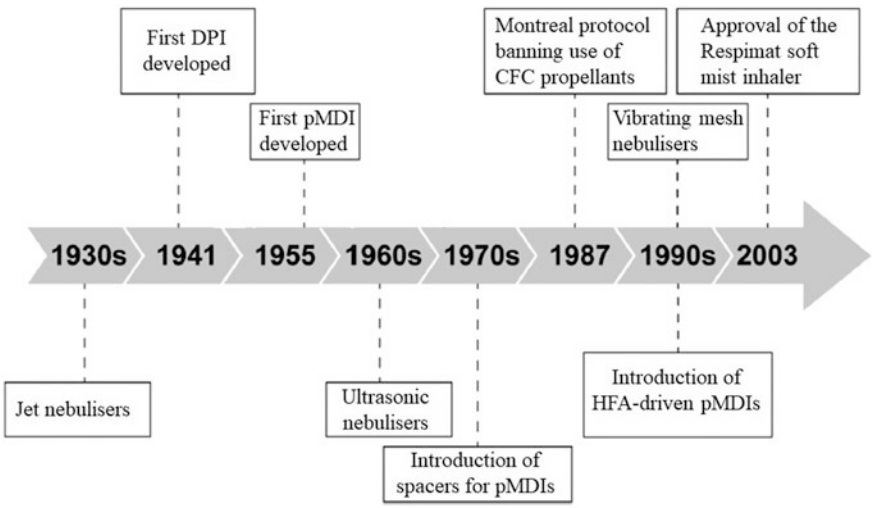

Fig. 1 Milestones in the development of inhaler therapy. Adapted from Iwanaga et al. (2019)

2 Current Inhalation Delivery Systems

Available inhalation devices include pMDIs (used with or without a spacer), DPIs, nebulisers and soft mist inhalers (SMIs). Each device type is associated with advantages and disadvantages, and these are summarised in Table 1.

2.1 The Development of Modern HFA pMDIs

First introduced in the 1950s, the pMDI is the inhaler most commonly used for drug delivery in the treatment of patients with asthma or chronic obstructive pulmonary disease (COPD). The pMDI consists of an aluminium canister, lodged in a plastic support, containing a pressurised suspension or solution of micronised drug particles dispersed in propellants (Roche and Dekhuijzen 2016). The key component of the pMDI is a metering valve, which delivers an accurately known volume of propellant, containing the micronised drug at each valve actuation. The operation principle of the present pMDIs remains similar to the original 1950s push-and-breath design:

Table 1 Strengths and weaknesses of each inhaler device type

	Strengths	Weaknesses
pMDI	Compact and portable Dose consistency Multidose Wide range of therapies	Contains propellant Requires good coordination of actuation and inhalation
pMDI + spacer	Easier to coordinate large drug doses delivered more conveniently Higher lung deposition than a pMDI alone less oropharyngeal deposition	Less portable than a pMDI plastic spacers may acquire static charge additional cost to a pMDI
DPI	Compact and portable Multidose Wide range of therapies No propellants Breath actuated (no coordination needed)	Moisture-sensitive Requires a minimum inspiratory flow Requires steps for preparation Dose inconsistency
SMI	Portable and compact multidose device High lung deposition does not contain propellants	Not breath actuated Requires some coordination of actuation and inhalation Requires priming before first use
Nebulisers	No specific inhalation technique required Vibrating mesh is portable and does not require an outside energy source High lung deposition (mesh nebulisers)	Jet and ultrasonic nebulisers require an outside energy source Treatment times can be long Performance varies between nebulisers Risk of bacterial contamination

pMDI pressurised metered-dose inhaler, *DPI* dry powder inhaler, *SMI* soft mist inhaler

pressing the bottom of the canister into the actuator seating causes decompression of the formulation within the metering valve, resulting in an explosive generation of a heterodisperse aerosol of droplets that consist of tiny drug particles contained within a shell of propellant (Fig. 2). The latter evaporates with time and distance, which reduces the size of the particles that use a propellant under pressure to generate a metered dose of an aerosol through an atomisation nozzle (Roche and Dekhuijzen 2016). Initially, pMDIs used chlorofluorocarbon (CFC) propellants, which were superseded by hydrofluoroalkane (HFA) propellants due to growing environmental concerns that CFC propellants were causing irreparable damage to the ozone layer in the atmosphere. Hydrofluoroalkanes were identified as a potential alternative, since they were considered inert with respect to environment. Although many of the physical properties of HFAs are similar to those of CFCs, direct translation of CFC formulations to HFA formulations was not possible. Historically, CFC formulations contained drug suspended in CFCs that were stabilised using surfactants. With the translation to HFA-based systems, it quickly became evident that the capacity for HFAs to solubilise these surfactants was not sufficient and thus a stable flocculated system could not be formed. Formulations of HFA-based pMDI systems are generally categorised as either suspension or solution technologies. Drug molecules conventionally used in pMDIs are not readily soluble in HFAs and thus require a co-solvent (Ganderton et al. 2002). Ethanol may be used as a co-solvent because it is miscible in HFAs and is also a good solvent for many hydrophobic pharmaceutical drugs. In general, solution-based pMDIs utilising volatile co-solvents result in higher fine-particle fractions, due to the small particle size of the dried aerosol. The particle size of solution-based pMDIs may be altered via the addition of non-volatile agents that are soluble in the HFA-co-solvent system; however, they will not evaporate during the aerosolisation process resulting in an increasing of final particle size (Buttini et al. 2014). Scanning electron microscopy images of particles generated from the glycerol-free and glycerol-containing formulations are shown in Fig. 3.

Some HFA-driven pMDIs have been extensively changed to obtain aerosol solution with small (mass median aerodynamic diameter ~1.3 μm) particle size (Lavorini et al. 2017). These pMDIs delivering small aerosol particles have shown

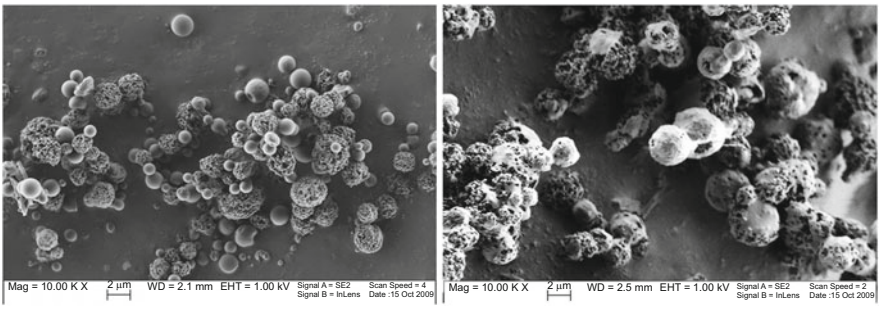

Fig. 2 The original pressurised metered-dose inhaler (pMDI) approved March 9, 1956 (left), and a modern pMDI with its main components (right)

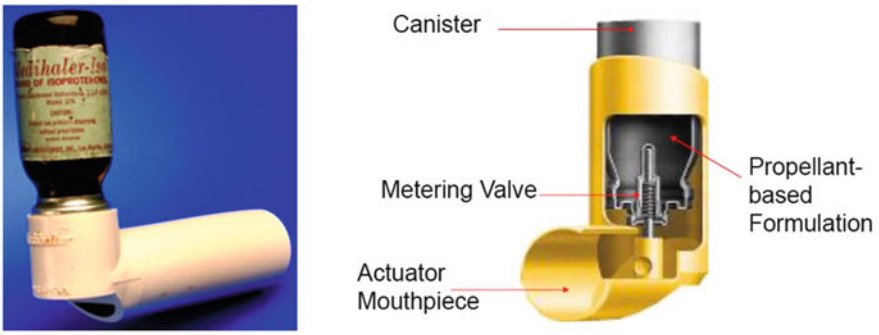

Fig. 3 Particles generated from the glycerol-free (left) and glycerol- (right) containing HFA pMDI formulations

to obtain a higher rate of pulmonary drug deposition than that achieved with the conventional pMDIs, i.e. those not emitting small aerosol particles (Lavorini et al. 2017). Generally, the velocity of the HFA spray is slower than that of the CFC, thus allowing a better distribution of the drugs along the respiratory airways and potentially making these devices more functional especially for elderly patients (Lavorini et al. 2016).

Correct use of the pMDI involves holding the inhaler in the correct position and performing a series of coordinated steps, and the complexity of this process can prove a challenge to some patients (Lavorini 2014). Suspension pMDIs also need to be shaken before use, a step commonly overlooked by both patients and healthcare professionals. In addition, for an efficient aerosol delivery to the lungs, pMDIs require slow, deep (i.e. an inspiratory flow rate of about 30 L/min roughly corresponding to a total inhalation time of 4–5 s) and steady inhalation starting just prior to device activation, with a subsequent short breath-hold of up to 10 s (Laube et al. 2011; Lavorini 2014). Unfortunately, most patients are not able to coordinate inhaler activation with inspiration and/or struggle to generate a deep enough inhalation, inhale too fast and/or fail to hold their breath for long enough, even after repeated tuition (Lavorini 2014). Importantly, misuse of pMDIs is associated with poorer asthma control, an increased number of exacerbations (Price et al. 2017) and worsening of COPD outcomes (Molimard et al. 2017).

To overcome the problems associated with poor pMDI use, spacers (Lavorini and Fontana 2009) and breath-actuated pMDIs are available (Lavorini et al. 2014). Spacers can be added to a pMDI to overcome problems with coordination and in doing so help to increase aerosol delivery to the peripheral airways. Spacers that feature a one-way inspiratory valve are termed valved holding chambers (VHCs). Spacers and VHCs can increase pulmonary deposition compared with pMDIs alone by reducing the velocity of the aerosol and filtering out larger, non-respirable particles (Lavorini and Fontana 2009). Breath-actuated pMDIs are useful for patients who struggle to time their inspiration properly, as they are triggered by airflow upon inspiration, although they still require an inspiratory flow rate of approximately 30 L/min and do not overcome the other disadvantages associated with pMDIs (Lavorini et al. 2014).

2.2 The Emergence of Modern DPIs

Much like the pMDI, DPIs are small, portable and widely available as either single-dose or multiple-dose devices (De Boer et al. 2017; Laube et al. 2011; Levy et al. 2019). At variance with pMDIs, all DPIs require a pre-inhalation dose-loading step to be completed successfully in order for them to function correctly. DPIs are actuated and driven by patient's inspiratory flow that drives the drug delivery; consequently, DPIs do not require coordination of inhaler actuation with inhalation thus resulting relatively simple to use for the majority of patients (De Boer et al. 2017; Laube et al. 2011; Levy et al. 2019). Most DPIs are formulated with their drug particles attached to excipient carrier molecules, such as lactose, or in the form of agglomerated pellets (De Boer et al. 2017). Consequently, DPIs are designed with an internal resistance that must be overcome by a forceful inhalation in order to generate a turbulent flow, de-aggregate the drug particles within, and produce fine particles for inhalation (De Boer et al. 2017; Laube et al. 2011; Levy et al. 2019). The currently available DPIs have varying internal resistance to airflow, which can be classified by the inhalation flow required to produce a 4 kPa pressure drop (Fig. 4). The force required to overcome the internal resistance, create a turbulent energy and generate an aerosol is the product of patient inhalation flow and the internal resistance of the device (Laube et al. 2011; Azouz and Chrystyn 2012). Subsequent lung deposition is a trade-off between generating sufficient power for particle de-aggregation and avoiding the increased oropharyngeal deposition that can occur at higher aerosol velocities (Azouz and Chrystyn 2012; De Boer et al. 2017). Therefore, a limitation of DPIs is their reliance on patients generating the necessary inspiratory force to de-aggregate the powder formulation into small respirable particles as efficiently as possible and, consequently, to ensure that the drug is delivered to the lungs (De Boer et al. 2017; Laube et al. 2011; Levy et al. 2019). The ability of certain patient populations to generate the required inspiratory force may impact an inhaler's efficacy thus substantially fine-particle dose delivered. Although most patients are capable of generating enough flow to

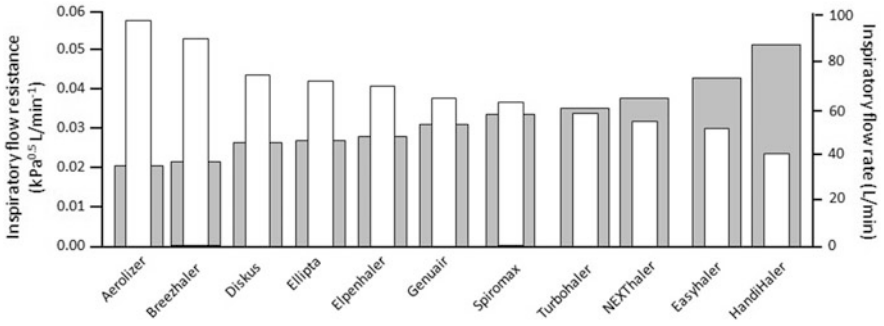

Fig. 4 Inspiratory resistance of dry powder inhalers (filled bars) and the corresponding flow (empty bars) required to achieve a 4 kPa pressure drop. See text for further details. Adapted from Lavorini et al. (2014)

operate a DPI efficiently, the need to inhale forcefully and, consequently, generate a sufficient inspiratory flow could be a problem for children aged <6 years or patients with severe airway obstruction (Laube et al. 2011).

Pulmonary administration of bronchodilators or corticosteroids as dry powders is primarily used to treat chronic obstructive airway diseases, such as asthma and COPD. However, in recent years an increasing interest has developed in the delivery of other types of drugs such as antibiotics to treat pulmonary infections. These medications have to be administered in higher doses (up to 200 mg) to achieve their therapeutic effect with limited amounts of excipients. As such, these types of formulations are regarded as "high powder dose drugs" (Sibum et al. 2018). Inhaled colistin (Colobreathe® Teva Pharmaceuticals Europe) and tobramycin (Tobi® Mylan Product Limited UK) are examples of high powder dose antibiotics for the treatment of cystic fibrosis patients. Notably, the efficacy of these inhaled antibiotics depends on the capability of the DPI device to load a consistent amount of powder and to modulate its release. For instance, the RS01 DPI (Plastiape Osnago, Italy), due to its delivery mechanism based on the spinning of the capsule, has shown to control the amount of a tobramycin powder emitted during the inhalation (Buttini et al. 2018a, b). Other DPIs releasing high dose of antibiotics are the Podhaler® (Mylan Product Limited UK), the Turbospin® (Forest Laboratories UK) the Orbital® (Pharmaxis, Australia), the Twincer® (Indes, the Netherlands) and the Cyclops® (PureIMS, The Netherlands) (Hoppentocht et al. 2015; Sibum et al. 2018).

2.3 Nebuliser Systems and Soft Mist Inhaler

Nebulisers are devices that convert a liquid in solution or suspension into small easily inhaled droplets. Solutions are comprised of drug dissolved in a carrier liquid, whereas suspensions are comprised of solid drug particles suspended in the carrier liquid. It is far more appropriate to refer to the "nebuliser system" in its entirety in which several components, other than the nebuliser itself, play a significant role in influencing aerosol delivery and its characteristics (Dolovich 2002). Among the components, the most influential are the compressor or line feed applied to the nebuliser, the volume fill, the residual volume and the driving gas flow and the use of a face mask or mouthpiece. Each of these significantly affects the total amount of drug received by the patients during therapy, the rate of nebulised aerosol output and the particle size distribution. If any component of the nebuliser system is replaced by another, then the nebuliser system has changed, and the aerosol output characteristics will have been significantly altered (Dolovich 2002).

Basically, there are three types of nebulisers: the jet nebuliser, the ultrasonic wave nebuliser and the vibrating mesh nebuliser.

2.3.1 Jet Nebulisers

Jet nebulisers are by far the most common type of nebulisers used worldwide. A jet nebuliser is powered by a compressed gas (usually air or oxygen) that draws medication through a capillary tube in the nebuliser' chamber, shearing the liquid

formulation and directing it to a baffle-generating aerosol. Coarse droplets impact on baffles, while smaller droplets may be inhaled or may land on internal walls returning to the reservoir for re-nebulisation (O'Callaghan and Barry 1997; Boe et al. 2001). There are four different designs of jet nebuliser: jet nebulisers with a reservoir tube, jet nebulisers with a collection bag, breath-enhanced nebulisers and breath-actuated jet nebulisers (O'Callaghan and Barry 1997; Boe et al. 2001). Jet nebulisers with a reservoir tube provide continuous aerosol generation during the entire breathing cycle, causing the release of aerosol to ambient air during exhalation and anytime when the patient is not breathing. Jet nebulisers with a collection bag generate aerosols by continuously filling a collection bag that acts as a reservoir. Both the breath-enhanced and breath-actuated jet nebulisers are modifications of the "conventional" jet nebulisers specifically designed to improve efficiency by increasing the amount of aerosol delivered to the patient with less wastage of aerosol during exhalation (O'Callaghan and Barry 1997; Boe et al. 2001).

2.3.2 Ultrasonic Wave Nebulisers

Ultrasonic wave nebulisers use a rapidly (>1 MHz) vibrating piezoelectric crystal to produce aerosol particles (O'Callaghan and Barry 1997; Boe et al. 2001). Ultrasonic vibrations from the crystal are transmitted to the surface of the drug solution where standing waves are formed. Droplets break free from the crest of these waves and are released as aerosol. The size of droplets produced by an ultrasonic nebuliser is related to the frequency of oscillation (O'Callaghan and Barry 1997; Boe et al. 2001). Although ultrasonic nebulisers can nebulise solutions more quickly than jet nebulisers, they are not suitable for suspensions, and the piezoelectric crystal can heat the drug to be aerosolised which can limit its use for heat-sensitive molecules.

2.3.3 Vibrating Mesh Nebulisers

The most recent innovation was made around 2005, with creation of the ultrasonic vibrating mesh technology. These modern nebuliser systems have been developed to address some of the limitations of conventional air jet nebulisers, in particular the long treatment time and inefficient utilisation of drug. The integral component of mesh nebulisers is a vibrating mesh plate, or aperture plate, that possesses precision-formed holes that control the size and flow of the aerosolised particles. An attached or separate power supply provides electricity to a vibrating piezoelectric element. As the plate begins to vibrate, the drug passes through the holes, thus producing a dense aerosol at low flow rates (Skaria and Smaldone 2010; Dhand 2002). Vibrating mesh devices such as the AeroNeb® Pro (Aerogen, Ireland) and the eFlow® (Pari, Germany) have a number of advantages over other nebuliser systems: they have greater efficiency, precision and consistency of drug delivery and are quieter and generally portable (Skaria and Smaldone 2010; Dhand 2002). On the downside, they are significantly more expensive than other types of nebuliser and require a significant amount of maintenance and cleaning after each use to prevent build-up of deposit and blockage of the apertures, especially when suspensions are aerosolised, and also to prevent colonisation by pathogens (Dhand 2002).

2.3.4 The Respimat Soft Mist Inhaler

The development of the "soft mist inhaler" (SMI) falls within the definition of a nebuliser, as SMIs transform aqueous liquid solution to liquid aerosol droplets suitable for inhalation. However, at variance with the traditional nebuliser designs, they are handheld multidose devices that have the potential to compete with both pMDIs and DPIs in the portable inhaler market. At present, the only SMI currently marketed is the Respimat® (Boehringer Ingelheim, Germany). This device does not require propellants since it is powered by the energy of a compressed spring inside the inhaler. Individual doses are delivered via a precisely engineered nozzle system as a slow-moving aerosol cloud, hence the term "soft mist" (Dalby et al. 2004; Iwanaga et al. 2019). Scintigraphic studies have shown that, compared to a CFC-based pMDI, lung deposition is higher (up to 50%) and oropharyngeal deposition is lower (Dalby et al. 2004; Iwanaga et al. 2019). Respimat is a "press-and-breathe" device, and the correct inhalation technique closely resembles that used with a pMDI. However, although coordination between firing and inhaling is required, the aerosol emitted from the Respimat is released very slowly, with a velocity of approximately four times less than that observed with a CFC-driven pMDI (Dalby et al. 2004). This greatly reduces the potential for drug impaction in the oropharynx. In addition, the relatively long duration over which the dose is expelled from the Respimat (about 1.2 s compared with 0.1 s from traditional pMDIs) would be expected to greatly reduce the need to coordinate actuation and inspiration, thus improving the potential for greater lung deposition (Iwanaga et al. 2019).

3 Advances in Aerosol Science

3.1 Particle Sizing Techniques and In Vitro Measurements

An aerosol can be defined as a system of solid particles or liquid droplets that can remain dispersed in a gas, usually air (Bisgaard et al. 2002). Naturally occurring aerosols, as well as those emitted by clinical aerosol generators, almost always contain a wide range of particle sizes. Because the aerodynamic behaviour of an aerosolised particle is critically influenced by its mass, it is important to precisely describe the size distribution of aerosolised particles. In clinical studies, the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) are often used to characterise the dimension of an aerosol (Bisgaard et al. 2002). When the mass distribution of particles in an aerosol is fractioned and the cumulative particle distribution plotted as a lognormal distribution on probability paper, it often approximates a straight line. The MMAD represents the point in the distribution above which 50% of the mass resides, expressed as the diameter of a unit density sphere having the same terminal setting velocity as the aerosol particle in question, regardless of its shape and density (Bisgaard et al. 2002). The GSD is an indicator of the variability in particle diameters. If the particle size varies over a wide range (i.e. GSD $>$ 1.2), it is describe as having polydisperse particle distribution;

if the particles are of similar size (i.e. GSD < 1.2), the particle distribution is described as monodisperse. Monodisperse aerosols are usually encountered in research studies, whereas clinical aerosols are widely polydispersed (Bisgaard et al. 2002).

Particle size is an important factor in determining whether a particle will undergo nasopharyngeal, airway or alveolar deposition (Ziegler and Wacthel 2005). Methods for determination of particle size distribution are the light scattering or cascade impaction. The former is based on the principle that there is differential scattering of polarised light by particles of different size. In cascade impaction, particles at a set flow rate go through a series of apertures of decreasing diameter and impact on a series of plates if they fail to follow the air stream. The cascade impactor has been adopted as the method of choice for monitoring quality control in the manufacture of formulations for aerosol delivery, comparison of devices, and they can be used to estimate the amount of deposition in the respiratory tract. Characteristically, the cascade impactor is used to quantify the respirable fraction or fine-particle dose (usually the percentage of particles <5 μm diameter) as an estimate of lung delivery. Recommendations are available for assessment of particle size distributions and mass output of nebulisers, MDIs and DPIs. In vitro systems have been added to particle sizing devices in ways that more closely simulate the clinical scenario. Anatomic throats have been used with impactors instead of standard inlet manifolds. Radiolabelled aerosols have been delivered to anatomic lung models using simulated breathing patterns. Other measurements of "inhaled mass" from a nebuliser have used a patient or patient surrogate (piston pump) breathing from a nebuliser through filters.

Meaningful comparisons of the sizes of clinical aerosols should be compared only if obtained with identical techniques. Nevertheless, despite the technical difficulties encountered in measuring the size of polydisperse clinical aerosols, investigators have established that, when used with appropriate caution, data obtained by in vitro measurement of particle size do provide useful predictive data for subsequent clinical studies (Smaldone and Solomita 2009).

3.2 Imaging Aerosol Deposition Techniques

Several imaging modalities have been employed to quantify lung dose and the distribution of the dose of orally inhaled aerosols in vivo. Two-dimensional (2D or planar) imaging using gamma scintigraphy is the most widely used of these modalities. The gamma camera, invented by Anger in 1958, was used from the late 1970s to assess drug delivery to various organs, including the lungs. Two-dimensional gamma scintigraphy studies are accomplished using a single- or dual-headed gamma camera (Newman et al. 2003). The formulation to be tested is admixed with the gamma emitting radioisotope ^{99m}technetium, which serves as a surrogate for the drug. With this technique, total deposition should be assessed after identification of the right lung border and appropriate correction for tissue attenuation. Regional deposition should be quantified as a normalised outer/inner

deposition ratio and expressed as the penetration index (Newman et al. 2012). More recently, pulmonary drug delivery has been assessed with the three-dimensional imaging methods of single-photon emission computed tomography (SPECT) and positron emission tomography (Newman et al. 2003). SPECT is slightly superior to planar imaging for measuring total lung deposition. However, it is more complex to use, and for studies where total lung deposition is the endpoint, planar imaging is recommended. However, SPECT has been shown to be clearly superior to planar imaging for assessing regional distribution of aerosol and is the method of choice for this purpose. It therefore has applications in studying the influence of regional deposition on clinical effectiveness and also in validating computer models of deposition (Fleming et al. 2012).

3.3 Pharmacokinetics and Pharmacodynamics

Another approach to assessing respiratory drug delivery is to measure plasma levels of drug after absorption (pharmacokinetics) and to relate those levels to clinical efficacy and toxicity (pharmacodynamics) (Chrystyn 2001). The pharmacokinetic profile of a drug after inhalation may differ quite markedly from that seen after dosing by other routes of administration. Drugs may be administered to the lung to elicit a local action or as a portal for systemic delivery of the drug to its site of action elsewhere in the body (e.g. insulin). Some knowledge of pharmacokinetics is important for both locally and systemically acting drugs. For a systemically acting drug, the plasma concentration-time profile shares some similarities with drugs given by the oral or intravenous routes, since the plasma concentrations (after the distribution phase) will be in equilibrium with concentrations at the site of action. However, for a locally acting drug, such as an inhaled medication for the treatment of asthma or COPD, the plasma concentrations reflect its fate after it has been absorbed and removed from the airways, and not what is available to its site of action in the lung. Consequently, typical pharmacokinetic parameters which are determined from plasma concentration measurements (e.g. area under the curve, Cmax and tmax) may provide information on the deposition and absorption of drugs from the lung; however, the information from these parameters becomes more complicated to decipher for those drugs which are locally acting in the lung, and systemic levels are often used as a marker of toxicity (e.g. plasma levels of corticosteroids following inhalation). For instance, determination of pharmacokinetic profiles is difficult for inhaled drugs, because the low plasma levels require a sensitive assay and may be altered by drug absorbed from the gastrointestinal tract. In many cases, it is important to distinguish the relative contributions of lung and gastrointestinal tract absorption, as drug absorbed from the lung can be used as a surrogate for deposition. The influence of physiological and pathological factors needs also to be considered in the absorption of some inhaled drugs (Chrystyn 2001). The absorption of some hydrophilic drugs is influenced by the inspiratory manoeuver used during

initial inhalation of the drug and at later times after deposition. Similarly, the effects of smoking have been shown to increase lung permeability and increase the absorption of certain hydrophilic drugs (Chrystyn 2001).

4 Looking to the Future

Over the past decade, the efficiency of inhalers, as measured by total lung deposition, has increased from less than 10% to nearly 50% of the total dose, yet less than half the dose becomes available to the site of absorption (Hoppentocht et al. 2015). There is space for new technologies to improve these numbers, and pharmaceutical companies are continuously trying to innovate and improve on the existing inhalation technologies available. The incorporation of modern technology into inhaler devices is chiefly aimed at improving drug delivery, reducing device errors, improving patient adherence and monitoring and managing patients' disease state (Rogueda and Traini 2016).

New co-suspension technology uses low-density phospholipid particles to suspend micronised drug crystals in an HFA propellant, meaning multiple drugs can be administered via a single pMDI in a uniform manner (Ferguson et al. 2018). The low-density phospholipid particles increase the physiochemical stability of the drugs and can also reduce the effects of a shake-fire delay. In vitro and in vivo tests have shown highly reproducible, consistent drug delivery and effective lung deposition (Taylor et al. 2016). This was maintained across variations in flow rate, and drug delivery was constant under conditions of simulated patient handling errors, such as variable shake technique and delays between shaking and actuation (Doty et al. 2018).

One of the solutions envisaged to increase patient adherence to their therapies is the use of digital health solutions such as monitoring systems based on phone applications (apps) and electronic sensors. The first in-built inhaler monitoring technology was developed in the 1980s, mainly to assess adherence to medication, and this has evolved over the years to incorporate various other sensing functionalities (Kikidis et al. 2016). Development of the Smart Inhaler Tracker (Adherium) to store the dates and times of inhaler actuations led to the development of more sophisticated devices that incorporates a Global Positioning System (GPS) or functions capable of monitoring parameters such as inhalation flow and volume (Kikidis et al. 2016). The incorporation of dose-memory and dose-reminder functions in inhalers can have a positive effect on adherence and can increase confidence in self-management behaviour (Foster et al. 2017). In the 12-month STAAR study in children with asthma, for example, clinical review of electronic adherence monitoring data and dose reminders were shown to improve average adherence and reduce the number of courses of oral steroids and hospital admissions compared to non-review and no reminder function (Morton et al. 2017). In a randomised controlled trial in children with asthma, an electronic monitoring device with an audiovisual reminder function led to significant improvements in adherence to inhaled medications (Chan et al. 2015).

Digital health developments have also shown great utility in the management of device errors and are now able to provide detailed feedback on patients' device competence (Kikidis et al. 2016). The SmartMist™ (Aradigm) and MDILog™ (Westmed Technologies) have both included sensing capabilities to facilitate the assessment of inhalation technique. The MDILog™, which is widely used in clinical research, is designed to attach to the plastic casing of standard inhalers. The device includes an inhaler actuation sensor, as well as an accelerometer for the detection of inhaler shaking and a sensitive temperature sensor for the assessment of inhalation. Inhalation detection technologies can be used to coach patients on correct device technique. This kind of technology, along with other innovative e-health developments, such as mobile communication technology (mHealth), electronic reminders, telemedicine and inhaler tracker interventions, has the potential to reduce the resource burden on healthcare systems and provide optimal and personalised asthma management to patients (Bonini and Usmani 2018).

5 Conclusions

The pulmonary route of administration has proven to be effective in local and systemic delivery of miscellaneous drugs and biopharmaceuticals to treat pulmonary and non-pulmonary diseases. A successful pulmonary administration requires a harmonic interaction between the drug formulation, the inhaler device and the patient. Inhalation products are more complex compared to the conventional dosage forms: device and formulation interconnecting features should work together to aerosolise the drug and deliver it to the site of action. In this perspective, the development of inhalation products should be done using a Quality by Design approach in order to fully understand the interaction of the two product components and their contribution on the product performance enabling the minimisation of the patient errors during the device preparation and inhalation (Buttini et al. 2018a). In 2011 there were more than 230 different drug-device combinations available in Europe (Lavorini et al. 2011). Hoppentocht et al. (2015) list 32 different device technologies recently developed or in development currently devices technologies, and this count does not register recent generic devices. These numbers speak of inventiveness of technologists, but some of these inventions fail to translate into clinical improvements. Indeed, the biggest problem that accounts for the lack of desired effect or adverse outcomes is the incorrect use of the device. In addition, the myriad of devices and complex physics involved in the delivery often makes it difficult for clinicians to choose the right device for their patients. An ideal inhaler should deliver precise and consistent doses to a targeted region in the lungs and maintain the stability of the delivered drugs. It is also desirable that devices are small and simple enough to be easily used by patients. Dry powder inhalers are becoming more popular because of their ease of use; pMDIs are still facing challenges from the formulation and the design point of view. Nebulisers are being remodelled to broaden their applicability. Currently, there is no single device that fulfills the myriad of requirements to optimally deliver drugs having different physicochemical

properties, and therefore healthcare professionals need to fully understand the capabilities of each inhaler and relate that to the needs of the patient, according to their health status, to achieve the best therapeutic outcome.

References

Azouz W, Chrystyn H (2012) Clarifying the dilemmas about inhalation techniques for dry powder inhalers: integrating science with clinical practice. Prim Care Respir J 21:208–213

Boe J, Dennis JH, O'Driscoll BR et al (2001) European Respiratory Society guidelines on the use of nebulizers. Eur Respir J 18:228–242

Bonini M, Usmani OS (2018) Novel methods for device and adherence monitoring in asthma. Curr Opin Pulm Med 24:63–69

Buttini F, Miozzi M, Balducci AG, Royall PG, Brambilla G, Colombo P, Bettini R, Forbes B (2014) Differences in physical chemistry and dissolution rate of solid particle aerosols from solution pressurised inhalers. Int J Pharm 465(1–2):42–51

Buttini F, Rozou S, Rossi A, Zoumpliou V, Rekkas DM (2018a) The application of quality by design framework in the pharmaceutical development of dry powder inhalers. Eur J Pharm Sci 113:64–76

Buttini F, Balducci AG, Colombo G, Sonvico F, Montanari S, Pisi G, Rossi A, Colombo P, Bettini R (2018b) Dose administration maneuvers and patient care in tobramycin dry powder inhalation therapy. Int J Pharm 548:182–191

Chan AHY, Stewart AW, Harrison J et al (2015) The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. Lancet Respir Med 3:210–219

Chrystyn H (2001) Methods to identify drug deposition in the lungs following inhalation. Br J Clin Pharmacol 51:289–299

Dalby R, Spallek M, Voshaar T (2004) A review of the development of Respimat Soft Mist Inhaler. Int J Pharm 283:1–9

De Boer AH, Hagedoorn P, Hoppentocht M, Buttini F, Grasmeijer F, Frijlink HW (2017) Dry powder inhalation: past, present and future. Expert Opin Drug Deliv 14(4):499–512

Dhand R (2002) Nebulisers that use a vibrating mesh or plate with multiple apertures to generate aerosol. Respir Care 47:1406–1416

Dolovich MB (2002) Assessing nebulizer performance. Respir Care 47:1290–1301

Doty A, Schroeder J, Vang K et al (2018) Drug delivery from an innovative LAMA/LABA co-suspension delivery technology fixed-dose combination MDI: evidence of consistency, robustness, and reliability. AAPS PharmSciTech 19:837–844

Ferguson GT, Hickey AJ, Dwivedi S (2018) Co-suspension delivery technology in pressurized metered-dose inhalers for multi-drug dosing in the treatment of respiratory diseases. Respir Med 134:16–23

Fleming J, Bailey DL, Chan H-K, Conway J, Kuehl PJ, Laube BL et al (2012) Standardization of techniques for using single-photon emission computed tomography (SPECT) for aerosol deposition assessment of orally inhaled products. J Aerosol Med Pulm Drug Deliv 25(Suppl 1): S29–S51

Foster JM, Reddel HK, Usherwood T et al (2017) Patient-perceived acceptability and behaviour change benefits of inhaler reminders and adherence feedback: a qualitative study. Respir Med 129:39–45

Ganderton D, Lewis D, Davies R, Meakin B, Brambilla G, Church T (2002) Modulite: a means of designing the aerosols generated by pressurized metered dose inhalers. Respir Med 96(Suppl D):S3–S8

Hoppentocht M, Akkerman OW, Hagedoorn P, Frijlink HW, De Boer AH (2015) The Cyclops for pulmonary delivery of aminoglycosides; a new member of the Twincer™ family. Eur J Pharm Biopharm 90:8–15

Iwanaga T, Tohda Y, Nakamura S, Suga Y (2019) The Respimat® soft mist inhaler: implications of drug delivery characteristics for patients. Clin Drug Investig. https://doi.org/10.1007/s40261-019-00835-z

Kikidis D, Konstantinos V, Tzovaras D et al (2016) The digital asthma patient: the history and future of inhaler based health monitoring devices. J Aerosol Med Pulm Drug Deliv 29:219–232

Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, Everard ML, Horvath I, Navalesi P, Voshaar T, Chrystyn H, European Respiratory Society; International Society for Aerosols in Medicine (2011) What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J 37:1308–1331

Lavorini F (2014) Inhaled drug delivery in the hands of the patient. J Aerosol Med Pulm Drug Deliv 27:414–418

Lavorini F, Fontana GA (2009) Targeting drugs to the airways: the role of spacer devices. Expert Opin Drug Deliv 6:91–102

Lavorini F, Corrigan CJ, Barnes PJ, Dekhuijzen PR, Levy ML, Pedersen S, Roche N, Vincken W, Crompton GK (2011) Retail sales of inhalation devices in European countries: so much for a global policy. Respir Med 105:1099–1103

Lavorini F, Fontana GA, Usmani OS (2014) New inhaler devices – the good, the bad and the ugly. Respiration 88:3–15

Lavorini F, Mannini C, Chellini E, Fontana GA (2016) Optimising inhaled pharmacotherapy for elderly patients with chronic obstructive pulmonary disease: the importance of delivery devices. Drugs Aging 33:461–473

Lavorini F, Pedersen S, Usmani OS (2017) Dilemmas, confusion, and misconceptions related to small airways directed therapy. Chest 151:1345–1355

Levy ML, Carroll W, Izquierdo Alonso JL, Keller C, Lavorini F, Lehtimäki L (2019) Adv Ther. https://doi.org/10.1007/s12325-019-01066-6

Molimard M, Raherison C, Lignot S, Balestra A, Lamarque S, Chartier A, Droz-Perroteau C, Lassalle R, Moore N, Girodet PO (2017) Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. Eur Respir J 49. pii: 1601794

Morton RW, Elphick HE, Rigby AS et al (2017) STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. Thorax 72:347

Mudge J (1778) A radical and expeditious cure for a recent Catarrhous cough, 2nd edn. E. Allen, London, pp 131–147

Newman SP, Pitcairn GR, Hirst PH, Rankin L (2003) Radionuclide imaging technologies and their use in evaluating asthma drug deposition in the lungs. Adv Drug Deliv Rev 55:851–867

Newman S, Bennett WD, Biddiscombe M, Devadason SG, Dolovich MB, Fleming J et al (2012) Standardization of techniques for using planar (2D) imaging for aerosol deposition assessment of orally inhaled products. J Aerosol Med Pulm Drug Deliv 25(Suppl 1):S10–S28

O'Callaghan C, Barry PW (1997) The science of nebulised drug delivery. Thorax 52(Suppl 2): S31–S44

Price DB, Román-Rodríguez M, McQueen RB, Bosnic-Anticevich S, Carter V, Gruffydd-Jones K, Haughney J, Henrichsen S, Hutton C, Infantino A, Lavorini F, Law LM, Lisspers K, Papi A, Ryan D, Ställberg B, van der Molen T, Chrystyn H (2017) Inhaler errors in the CRITIKAL study: type, frequency, and association with asthma outcomes. J Allergy Clin Immunol Pract 5:1071–1081

Roche N, Dekhuijzen PNR (2016) The evolution of pressurized metered-dose inhalers from early to modern devices. J Aerosol Med Pulm Drug Deliv 29:1–17

Rogueda P, Traini D (2016) The future of inhalers: how can we improve drug delivery in asthma and COPD? Expert Rev Respir Med 10:1041–1044

Sanders M (2007) Inhalation therapy: an historical review. Prim Care Respir J 16:71–81

Sibum I, Hagedoorn P, de Boer AH, Frijlink HW, Grasmeijer F (2018) Challenges for pulmonary delivery of high powder doses. Int J Pharm 548:325–336

Skaria S, Smaldone GC (2010) Omron NE U22: comparison between vibrating mesh and jet nebulizer. J Aerosol Med Pulm Drug Deliv 23:173–180

Smaldone GC, Solomita M (2009) Predicting in vivo deposition in vitro. J Aerosol Med Pulm Drug Deliv 22:9–10

Stein SW, Thiel CG (2017) The history of therapeutic aerosols: a chronological review. J Aerosol Med Pulm Drug Deliv 30:20–41

Taylor G, Warren S, Orevillo C et al (2016) Pulmonary deposition of a novel LAMA/LABA co-suspension technology glycopyrronium/formoterol (GFF) MDI in healthy subjects. Eur Respir J 48:OA4834

Ziegler J, Wacthel H (2005) Comparison of cascade impactor and laser diffraction for particle size. J Aerosol Med 18:311–324