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Review Article

Theme: Advances in Formulation and Device Technologies for Pulmonary Drug Delivery
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Advances in Device and Formulation Technologies for Pulmonary Drug Delivery

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Abstract. Inhaled pharmaceuticals are formulated and delivered differently according to the therapeutic indication. However, specific device-formulation coupling is often fickle, and new medications or indications also demand new strategies. The discontinuation of chlorofluorocarbon propellants has seen replacement of older metered dose inhalers with dry powder inhaler formulations. High-dose dry powder inhalers are increasingly seen as an alternative dosage form for nebulised medications. In other cases, new medications have completely bypassed conventional inhalers and been formulated for use with unique inhalers such as the Staccato® device. Among these different devices, integration of software and electronic assistance has become a shared trend. This review covers recent device and formulation advances that are forming the current landscape of inhaled therapeutics.

KEY WORDS: dry powder inhaler; formulation; inhaled aerosols; metered dose inhaler; nebulizer.

INTRODUCTION

When Pfizer introduced the first commercial inhaled insulin (Exubera®) in 2006, it marked a major milestone for pulmonary drug delivery—the feasibility of inhalation as an alternate route of administration for treatment of systemic diseases (1-3). However, the subsequent withdrawal of Exubera® 2 years later due to poor reception, raised concerns about the future of pulmonary drug administration for systemic application (4). It demonstrated that, apart from the safety and efficacy of the product, other factors such as strong sales and marketing are essential for the success of novel inhaled products in the pharmaceuticals market. Nonetheless, there continues to be a strong interest in developing inhalable formulations for both local and systemic diseases, and current trends show novel applications that include needle-free vaccines, gene therapy, and targeted lung cancer treatments.

This review examines recent advances in inhaler device and formulations, trends in development of inhaled aerosols, and the role of inhaled therapeutics in addressing current and future therapeutic needs.

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DEVICES

Dry Powder Inhalers

Dry powder inhalers (DPIs) are categorized as either passive or active devices depending on the source of airflow for powder aerosolization. These devices are further subdivided as single-dose reusable, multidose, and single-use devices.

Passive Devices

A patient's inspiration provides the main source of energy to aerosolize the drug powder in passive devices. Currently, these are the primary type of DPI devices on the market. Most passive inhalers consist of an air inlet, dispersion chamber, and mouthpiece, but the dispersion mechanisms vary to a large extent. For the traditional passive inhalers, powders are entrained into the dispersion chamber and airflow disperses the powder bed into inhalable aerosols, which can be inhaled by the patient (5). This process depends on the balance between interparticulate cohesive/adhesive forces and the de-agglomeration forces generated by the airflow (6). The fundamental mechanisms of airflow-induced dispersion are not well understood but are generally believed to be the combined effects of air turbulence and powder impaction (6-9). Therefore, adding de-agglomeration enhancers (such as a 3D array of rods (10), oscillating bead (11), or impaction grid (12)) can be a straightforward and cost-efficient way to improve the aerosol performance. As an example, adding a 3D array of rods in the mouthpiece of a Handihaler chamber improved fine particle fraction (FPF) of the emitted dose from 87.6 to 97.3% for a submicron excipient enhanced growth (EEG)

formulation dispersed at a flow rate of 45 L/min (10). Computational fluid dynamics (CFD) analysis showed that enhanced turbulence and particle exposure time contributed to the improved de-agglomeration (10, 13).

Reverse-flow cyclone technology was applied to develop the Conix™ passive DPI device (14). The Conix™ utilizes a vortex, with high velocities and energy that produces extra shear and impaction forces to de-agglomerate the powder. A unique feature of Conix™ is that the dispersed fine particles will be inhaled while the lactose carriers with larger sizes will be retained in the dispersion chamber to promote de-agglomeration. The FPF (in this instance only, defined as particles with a mass median aerodynamic diameter (MMAD) <3 μm) of the Conix™ for a lactose-based combination formulation was shown to be 41.8% for fluticasone propionate and 40.5% for salmeterol xinafoate, which were much higher than that of the comparative Diskus DPI device (14% for fluticasone propionate and 12.3% for salmeterol xinafoate) (14).

Newer inhalers may not rely solely on the inspiration airflow to disperse the powder. A mesh-sieving mechanism was applied to develop a single-use DPI based on the ActiveMesh™ technology (15). During aerosolization, a mesh strip with the powders packed inside the mesh oscillates and beats to push the powder through the small mesh holes, thereby de-agglomerating the powder (15). Although the oscillating and beating motion of the strip are driven by inspiration, complex mechanical forces are involved to achieve better powder dispersion. Similarly, a fluttering motion driven by airflow provided the major dispersion forces for another device (16). In this device, powders are coated in an aeroelastic film and placed in the middle of the inhaler with one end under tension. Upon inhalation, particles were shaken from the film by its fluttering action. The flutter-based devices achieved FPF values in the range of 40–60% at 60 L/min for ciprofloxacin powders (16).

The major issue with passive devices is flow-dependent de-agglomeration driven by inspiration. Powder dispersion from earlier passive inhaler designs was significantly affected by the flow rate (17, 18). More recent designs have minimized flow dependency, but it remains an issue at low flow rates. For patients with compromised lung functions, active devices are more suitable to deliver pharmaceutical aerosols to the lungs.

Active Device

In active DPI devices, external energy sources disperse the drug powder; hence, aerosolization efficiency is independent of inspiration. Dispersion can be achieved by compressed air, electrical vibration, or mechanical impeller. FPF values greater than 70% have been demonstrated for an active Aspirair® device that uses compressed air as the dispersion source (19). In this device, powder is prepacked in the foil and can be loaded into the inhaler just before use. Active dispersion mechanism can also be used for multidose DPIs. For an active multidose DPI, the aerosol performance showed satisfactory FPF values in the range of 50–70% for several pharmaceuticals—spray-dried insulin, phenylalanine, nitrendipine, and phenylalanine-labeled fluorescein isothiocynate (20). Besides compressed air, a piezoelectric system has also been employed by the MicroDose DPI. *In vitro* aerosolization tests demonstrated an FPF of 57% (21).

Active devices can be useful supplements to the current popular passive devices. The aerosolization performance is consistent and independent of the patient's inspiration efforts. This feature is particularly critical to the inhalation treatment for patients with limited lung function or much reduced lung volume, such as children, the elderly, and those with cystic fibrosis (CF). Although recent designs are portable with simpler operating procedures, cost remains a barrier.

Multidose Device

Multidose inhalers include multi-unit and reservoir types. In multi-unit DPIs, powders are packed in the individual blister or foil, whereas the dose of the reservoir type is dispensed by a metering valve. The multi-unit devices may offer better protection against moisture and light with an additional separate package for each dose unit. A mechanical or electrical dose counter is essential to indicate the remaining dose.

NEXThaler® is a multidose inhaler with a simple operation procedure. A dose can be administered in less than a minute, requiring the patient to only open the lid, inhale from the mouthpiece, and close the lid. The device is equipped with an innovative full-dose feedback system incorporating a novel breath-actuated mechanism. This system ensures that the dose counter is only activated once the full dose is emitted (22). A multidose inhaler intended to deliver low-dose (<100 μg) pure drug powders as was recently reported (20). The device utilizes a rotating disk with separate holes (12–64 doses) filled with the drug powder. The multidose disk can be loaded into the inhaler chamber with only one drug pocket in the air passage at a time. An air compressor is used to actively disperse the drug powder and the FPF values of the selected spray-dried powders (insulin, phenylalanine, nitrendipine, and phenylalanine-labeled fluorescein isothiocynate) were in the range of 50–70% (20).

Single-Dose Reusable Device

Single-dose reusable devices have each dose prepared in a separate single unit such as a capsule or blister. During administration, a single-dose unit is loaded into the inhaler, aerosolized for patient inhalation, and then discarded. Designing the device with the formulation as a separate entity minimizes its dimensions. Additionally, the powder mass in each unit is flexible, permitting use of the same device for both low- and high-dose therapies.

Medications requiring high doses are typically delivered by single-dose reusable devices rather than multidose inhalers, as packaging high doses into the latter would result in bulky, impractical devices. Both approved antibiotic DPIs of TOBI® Podhaler™ (tobramycin) and Colobreathe® Turbospin® (colistimethate sodium) are examples of these reusable devices with the powder prefilled in capsules. These two devices are designed specifically to deliver high drug doses, which may exceed 100 mg, in multiple inhalations. In the TOBI® Podhaler™, each dose (112 mg) is packed into four capsules, with 28 mg of drug dose in each capsule (23). During administration, the patient inhales the four capsules sequentially. In the Colobreathe® Turbospin® device, a powder mass of 125 mg is filled into a single capsule (24). Repeated inhalations are typically required to empty the capsule. Similarly, the

Orbital® DPI delivers 200 mg of powder and requires multiple inhalations (25). Emitted doses greater than 90% could be obtained for the Orbital® with less than 10 inhalation cycles for spray-dried ciprofloxacin or mannitol powders (25).

Single-Use Inhalers

For less frequent inhaler therapies or certain infectious diseases, single-use inhalers are suitable. The TwinCaps® DPI by Hovione is a typical example of such a disposable device and useful for single-dose (40 mg) treatment. It is used for delivering powder aerosols of a long-acting neuraminidase inhibitor, laninamivir (Inavir®) for the treatment of influenza. Alternatively, it might also be applied to vaccine delivery via inhalation (15). Single-use inhalers minimize the risk of spreading infection. The antibiotic colistin was delivered by a disposable device (Twincer®) for the treatment of chronic infections in CF patients (26). The Twincer® is designed based on the multiple air classifier technology (27) with a relatively high aerosol performance (FPF of 58–67%) compared to other lactose-based DPI formulations (28, 29).

Cost and proper device use are crucial for single-use inhalers, and is facilitated by the simple design of the aforementioned devices. Specifically, the Twincer® has three plastic parts and the TwinCaps® has only two, making the manufacturing easier and cheaper. As patients do not regularly use these disposable devices, the operation protocol should be simple to promote patient adherence.

Pressurized Metered Dose Inhalers

Pressurized metered dose inhalers (pMDIs) are sometimes regarded as outdated devices, with relatively minor improvements over the past 50 years. Nonetheless, the recent introduction of compact and convenient breath-actuated, breath-coordinated, and velocity-modifying device hardware has successfully addressed issues pertaining to actuation coordination, inefficient fine particle range, and limited delivered dose (30). While it faces tough competition from DPIs and novel soft-mist inhalers, the rejuvenated pMDI has retained its relevance due to its affordability, which is especially important in the emerging markets. Three key advances in pMDI technology are reviewed, namely, dose counters, breath-actuated devices, and electronic adherence measures. Other pMDI hardware technologies are further elaborated on by Stein *et al.* (31).

Dose Counters

In 2003, the US Food and Drug Administration (FDA) issued recommendations emphasizing the importance (but not mandating) integrated dose counters on new pMDIs in development (32). Patients often struggle to recognize when the pMDI canister becomes empty, as the opaque aluminum canister makes it impossible to assess by eye. Therefore, dose counters provide the only accurate and practical method of ascertaining the number of remaining doses. Without a counter, the pMDI may be used beyond the recommended number of doses and deliver suboptimal treatment that could be life-threatening. Dose counters rely on either an active event of firing such as sound, temperature, or pressure change (direct) or on canister movement/thumb pressure (indirect). Direct counters may fail less, being linked to the actual delivery of a dose, but are technically harder to achieve in comparison to the indirect counters (30). At present, the only marketed products that have integrated dose counters are ProAir® HFA (Teva Pharmaceutical Industries) and Ventolin® HFA (GlaxoSmithKline) (33).

Breath-Actuated pMDIs

Breath-actuated pMDIs have made it possible to overcome poor coordination, which is a common and critical mistake in pMDI technique (34). Although the first breath-actuated pMDI was introduced by 3M in the early 1970s (Autohaler) (35), newer versions have followed. A recent example, the K-Haler™ (Clinical Designs Ltd), is relatively simpler in construction and can be used in a number of ways. The unique patented K-valve™ is a kinked plastic tube, into which the metered dose is discharged from the standard metering valve of a conventional pMDI. Inhalation straightens the tube which releases the dose. An optional dose counter (Helix™, Clinical Designs Ltd) may also be integrated into the design. Older breath-actuated pMDI devices have been described by Bell and Newman (30).

Electronic Adherence Logging

Finally, electronic monitors are becoming key components in interventions that improve adherence. The SmartMist (Aradigm Corporation) was one of the first electronic monitors for pMDIs that was marketed in 1997 for a very brief time. It was a large device, which accommodated the pMDI and actuator with only the mouthpiece exposed, and provided immediate feedback on inspiratory flow (in order to minimize inhaler technique errors) and recorded the time and date of every actuation (36). More recently, commercially available inhaled medication monitors include the DOSER™ (MediTrack Products), MDILog (Westmed Technologies Inc.), and Smartinhaler (Nexus 6). The DOSER™ is a circular LCD screen that attaches to the top of a pMDI to track actuated doses. It acts somewhat like an external dose counter, storing up to 30 days of data on the number of daily inhalations and indicating the remaining dose in the canister. Similarly, the MDILog is also attached to the top of a pMDI. It contains a computer chip that records the date and time each time the device is actuated. Alternatively, the Smartinhaler is a digital cover that replaces the original pMDI plastic casing. It records the date and time when a dose is actuated, and data can be downloaded to a computer.

These three electronic adherence monitors have been compared by Ingerski *et al.* (37). In conjunction with improvements in software development and innovative apps on mobile cellular devices, remote downloading of data may allow clinicians to identify and problem-solve possible adherence-related difficulties. With advances in medicine, and continued awareness of the significance of adherence, electronic monitors could become a permanent fixture in future clinical practice.

Nebulizers

Nebulizers are particularly useful for diseases that require high pulmonary doses (e.g., CF) and patients who are unable to coordinate or achieve flow rates necessary for use of other inhalation devices (e.g., children) (38).

Types of Nebulizers

Three main types of nebulizers are available, which are categorized according to the mechanism used to convert the drug solution or suspension into an inhalable aerosol. Jet nebulizers (e.g., Pari LC Sprint) remain the most common and use compressed gas to disperse the liquid medication into aerosol droplets. However, treatment times are long, the air compressors are heavy and noisy, and mechanical shear forces can affect certain medications (39). Alternatively, ultrasonic nebulizers (e.g., Poly Green KN 9210) operate silently and are much more portable. The major drawback is a tendency to heat liquid in the reservoir making it inappropriate for thermal-labile medications such as proteins (40, 41). Vibrating mesh nebulizers (e.g., Pari eFlow Rapid) are the newest technology, which overcome the disadvantages of both jet and ultrasonic nebulizers, with rapid treatment times, minimal residual volume, and greater aerosol delivery. Nonetheless, their high cost remains a barrier to greater patient use (40, 42).

A principle flaw of these devices is that aerosol is generated continuously throughout the patient's entire respiratory cycle. Thus, a large proportion of medication is lost during exhalation, resulting in inefficient aerosol drug delivery and variable dosing. This may be controlled by mechanical means as seen with breath-enhanced or breath-actuated jet nebulizers that limit the majority of aerosolization to the patient's inspiratory phase (43). More recently, much greater control of nebulized aerosol delivery has been afforded by the coupling of software control with nebulizers (44, 45). In this combination, aerosolization is precisely timed to certain periods of the respiratory cycle and patient inhalation pattern are optimized leading to accurate high-dose pulmonary drug deposition in a much shorter time. Here, we provide an update on two current, commercially available examples which are the Activaero AKITA® and Philips I-Neb® nebulizer systems.

AKITA®

The AKITA® system contains a SmartCard electronic control unit with an air compressor which is coupled to either a jet or mesh nebulizer (45). The SmartCard software operates the air compressor unit to regulate a patient's inhalation, such that the AKITA® system can accurately control dose delivery and target nebulized aerosol to specific regions of the lungs (46, 47). This was demonstrated in a recent clinical study using dornase alpha, in which two different lung deposition patterns were achieved by differentially programming the AKITA® system, and treatment response increased with small airway deposition (48). Additionally, this targeted dosing has been shown to minimize inter- and intrapatient dosing variability which could significantly improve reproducibility for future nebulizer clinical trials (43, 49). Combined with the minimal residual volume of the mesh nebulizer, the AKITA® system ensures delivery of precise doses while minimizing systemic side effects.

A recent area of interest has been the implementation of the AKITA® system in the treatment of asthma in children. In an open-label, pilot trial (24), budesonide was administered by jet nebulization with or without control by the AKITA® system to children with asthma. Compared to regular jet nebulizer, the AKITA® system achieved similar or better efficacy and was well-accepted by children and their parents. It also reduced the time for inhalation as well as the required nebulized doses (24). The significance of these results is reflected in a study by Hofmann *et al.* (23) that found the AKITA® system to be an excellent driver of patient adherence, achieving an exceptional 92% adherence rate in children. This also highlighted the usefulness of the system's adherence logging software for checking by doctors and clinical trial (23). Beyond adherence, clinical efficacy could also be improved by controlling specific regional deposition. Targeting of small airways in asthma by inhaled medications can be challenging. Therefore, there may be an opportunity to reduce side effects associated with systemic steroid uptake in patients with severe asthma who are not sufficiently controlled using regular inhaled therapies, systemic steroids are often indicated and associated with side effects (50). By programming the AKITA® system to target the peripheral airways, Janssens *et al.* (50) found that systemic steroid exposure in children with severe asthma was reduced as were hospital admissions. Thus, AKITA®-aided nebulization of inhaled drugs has the potential to considerably improve treatment of airway disease in children. However, the AKITA® system lacks true portability due to the bulkiness of the combined compressor and software unit.

I-Neb®

In contrast, the I-Neb® combines both an Adaptive Aerosol Delivery (AAD) software control unit and a mesh nebulizer into a portable device (40). Without the external air compressor of the AKITA system®, the AAD software instead uses a vibratory feedback mechanism that guides the patient towards an optimal breathing profile termed the targeted-inhalation mode (TIM). Alternatively, the device can also adapt aerosolization to a patient's tidal breathing (tidal breathing mode or TBM), although this is less efficient.

Recent published literature on the I-neb has thus focused on the mode of breathing, specifically the unique TIM breathing pattern to improve lung deposition and subsequently reduce treatment time. Using radiolabelled diethylenetriaminepentaacetic acid in saline, Nikander *et al.* (51) demonstrated higher total (73 vs 63%, for TIM and TBM, respectively) and peripheral (35 vs 29%, for TIM and TBM, respectively) lung deposition when using TIM instead of TBM. This translated to considerable reductions in treatment time (3.0 vs 4.7 min, for TIM and TBM, respectively). This was also observed in a recent *in vitro* study utilizing a breathing simulator, which found that an I-Neb® operated in TIM reduced treatment time with α1-antitrypsin by a third, compared to use in TBM (52). Similarly, in a study by Denyer *et al.* (53), in patients with CF using the I-Neb, a 40–50% reduction in treatment time for patients (12–57 years) was observed for

those who chose to use TIM instead of TBM. In addition, although the device was used in a domiciliary setting, correct use of the I-neb, as recorded by the device's patient logging system, was a surprising 97.6%. A similar level of treatment time shortening and increased adherence was observed when using TIM in a study with children (5–16 years) with CF (54). Highlighting the efficiency of the I-Neb®, up to fivefold decreases in doses were found necessary to match the lower deposition efficiency of jet nebulizers (55). These recent studies demonstrate that the I-neb should preferentially be operated in TIM where possible to gain maximum benefit in efficacy and adherence. However, it also emphasizes the need for guidelines standardizing doses between the existing number of different nebulizer devices.

Other Inhalation Devices

Respimat®

The Respimat® Soft Mist™ Inhaler (SMI) utilizes a compressed spring to generate a low-velocity aerosol over a period of approximately one second. Compared to the equivalent pMDI or DPI dosage form, a greater proportion of the emitted dose from the Respimat® deposits in the lungs, necessitating a lower dose to maintain similar efficacy and safety (56, 57). For example, compared to 18 μg of the tiotropium administered using the Handihaler® DPI, equivalent efficacy is achieved with 5 μg of tiotropium administered by the Respimat® (58). Recent applications of the Respimat® SMI are on medications targeted towards asthma and chronic obstructive pulmonary disease (COPD), including an ipatropium bromide/albuterol combination (59), tiotropium (60), budesonide (57), and olodaterol (61). For example, the device has been used as an environmentally friendly alternative for the ipatropium bromide/albuterol combinations that were previously delivered by older chlorofluorocarbon (CFC)-propellant pMDIs (59). In part due to its ease of use, patient satisfaction has been shown to improve in patients with asthma and COPD, when their existing inhaler was replaced with the Respimat® (56, 57). However, whether the considerably higher patient satisfaction and preference for Respimat® compared to their conventional pMDI and DPI counterparts will translate to improved patient adherence, remains to be established (56).

Interestingly, recent literature on the device has mostly centered around calls in 2012 for Respimat®-administered tiotropium to be removed from the international market (62). A number of systematic reviews and meta-analyses raised concerns that tiotropium delivered by the Respimat® increased the risk of cardiovascular and "all-causes" deaths compared to the Handihaler® or placebo (63). It was suggested that even at the lower doses adjusted for use with the Respimat®, greater systemic exposure of tiotropium might still occur (62). However, increased adverse effects or mortality was not recorded in other clinical trials (58, 64), and pharmacokinetic studies did not show increased tiotropium exposure (60). Various authors discussed reasons for or against the removal of Respimat®-administered tiotropium from general use (65-70). However, with the release of results in 2013 from a large clinical trial (Tiotropium Safety and Performance in Respimat® (TIOSPAR)) designed to address some of these issues, safety concerns relating to Respimat® tiotropium appear to have lessened (71). The study found no significant differences in deaths between patients administered tiotropium by the Handihaler® or Respimat®. Nonetheless, these previous concerns related to tiotropium Respimat® demonstrate the need for understanding the unique pharmacokinetics of SMIs and the potential need for dose adjustments when adopting existing inhaler formulations.

Staccato®

The Staccato® device is a single dose, disposable unit that utilizes a unique thermal system to rapidly heat and vaporize a thin film of drug (72). As the patient inhales, the vapor condenses to form pure drug particles that deposit in the alveolar regions for swift systemic absorption. These aerosol particles have distinct properties. Dinh *et al.* demonstrated that loxapine aerosol droplets had an optimal MMAD of 2 μm mass which was independent of most other test conditions such as temperature, humidity, and device orientation. This resulted in a consistently high FPF between 85 and 90% (73). In a separate study (72), it was found that even as inhalation airflow rate increased, oropharangeal deposition remained low and consistent at around 11%. Low throat deposition has previously been shown to be the principal factor behind low interdose variability, a desirable attribute for good clinical efficacy with inhaled aerosols, with fine drug particles leading to higher peripheral lung deposition and systemic absorption for many small-molecule drugs (74). Thus, the Staccato® device presents a unique approach to inhaled medications with drug particles that have systemic absorption.

Currently, the device is used to administer the antipsychotic loxapine in the treatment of agitation in adults diagnosed with schizophrenia or bipolar disorder I (75). The combination has performed well in a number of multicenter clinical trials in schizophrenic and bipolar patients having a rapid therapeutic effect with a good safety profile (76-78). For example, in a randomized placebo-controlled clinical study by Allen *et al.* (78), 5 or 10 mg of loxapine was administered by the Staccato® inhalation device to agitated patients with schizophrenia or schizoaffective disorder. Rapid improvement was observed in these patients and treatment was well-tolerated. The use of the device might also assist in reducing adverse effects and loss of autonomy often associated with this class of medication. As a result of these promising clinical trials, inhaled loxapine delivered by the Staccato® device was approved by the FDA in late 2012, then in early 2013 by the European Medicines Agency (EMA) (75, 79). The device and existing clinical evidence are well-reviewed by Currier *et al.* (79) and Citrome (75).

AERx®

The Aradigm AERx® system is a software-controlled, handheld device that extrudes a drug solution through laser-drilled nozzles to form respirable droplets with a narrow size distribution. Both the dose and nozzles are contained on a single disposable strip (42). The software guides the patients towards an optimal inhalation manner and also records

adherence (80). The device was initially developed for delivery of inhaled insulin by Aradigm and Novo Nordisk, reaching phase III trials (81). However, it was discontinued following Pfizer's termination of their competing product (Exubera®) in 2007 due to poor sales and acceptance (82). The device has previously been tested with some success for delivery of rhDNase in patients with CF (83). It has also been investigated for the management of pain, in particular with inhaled morphine which has so far been found to have similar or better efficacy when compared to oral or parenteral administration (84). More recently, the dose proportionality design of AERx® has seen it trialed for nicotine replacement therapy, with device-generated aqueous nicotine aerosol shown to eliminate cravings for at least 4 h (85, 86). It remains to be seen whether these applications will eventually be commercialized.

FORMULATION

DPI

Recent DPI Formulation Trends

The development of DPIs is following three main trends: (1) enhancing delivery using nanoparticles, (2) prolonging activity of therapeutics with polymeric carriers, and (3) expanding applications to vaccines as a needle-free alternative. These trends and others are discussed extensively by Weers *et al.* (87).

Nanoparticles. The use of nanoparticles in DPI formulations for pulmonary drug delivery continues to be a hot topic (88). In comparison to micronized salbutamol sulfate, nanoparticles of the same drug was found to have significantly less particles impacted in the oropharyngeal region and higher peripheral deposition in humans, which suggested a greater local bioavailability for a sustained period of time, by virtue of their smaller size (89). Hence, nanoparticles provide an attractive particle engineering technique for developing formulations for inhalation (90). Approaches to produce drug nanoparticles fall under two major categories: (1) top-down (wet milling and high pressure homogenisation) (91) and (2) bottom-up (precipitation and solvent evaporation) (92, 93). A notable formulation technique is the formation of nanomatrix particles, a microparticle system made of aggregated nanoparticles suitable for inhalation. Interestingly, Kwok *et al.* (94) found that it was possible to control surface roughness of these microparticles by manipulating the primary sizes of the nanosuspension. The results for a model protein (lysozyme) showed that an increased surface roughness, with the use of larger nanoparticles, enhanced aerosol performance by reducing cohesive forces. The nanomatrix is very versatile so a number of active pharmaceutical ingredients have already been incorporated. These include budesonide (95, 96), ciprofloxacin (97), fluticasone in combination with salbutamol (98), insulin (99, 100), lung contrast agents (101, 102), nifedipine (103), and paclitaxel (104).

Polymeric Carriers. Micro- and nanopolymer carriers are a novel concept for controlled release due to prolonged retention in the lung (105-111). The physicochemical properties (size, shape, surface chemistry, and bioadhesive properties) are key parameters to consider in designing formulations that bypass the clearance mechanisms of the lung (112). Current strategies have included encapsulation through antisolvent precipitation and spray drying. A number of polymers may be chosen based on criteria such as biocompatibility and degradability (113). Poly(-lactide-co-glycolide) (PLGA) is the most extensively used due to its low toxicity (114, 115). However, the slow degradation rate (weeks to months) could lead to unwanted accumulation in the lungs, particularly if frequent dosing is required (116, 117). In addition, the low affinity of drugs to the polymeric matrix often leads to weak binding that is accompanied by fast release rates (118, 119). Other polymers with faster degradation rates have been synthesized, by grafting short PLGA chains onto charge-modified poly(vinyl alcohol) (PVA) backbones, to overcome this problem (120, 121). In this way, degradation can be tailored through modifying the PLGA chain length and degree of charge substitution which modulates the degradation from a few hours up to several weeks. Composite particles with the addition of excipients such as surfactants or stabilizers (122) can also modify surface charges, degradation rates, stability, toxicity, and biological activity. Despite this, toxicity concerns remain a subject of intense research. The evidence to date has found that the toxicity depends on the degradability, chemical composition, particle size, and local concentration (123, 124).

Expanding Applications of Inhalation Drug Delivery—Needle-Free Vaccines. The future of immunization relies on research for vaccines that are simpler to administer, will survive transport even without refrigeration, and will provide a more substantial and long-lasting immune response. Inhaled dry powder vaccines could be particularly useful in remote areas as its application would not require a trained medical person. An aerosolized measles vaccine is being pursued for incorporation into the World Health Organisation's Expanded Programme of Immunization (125, 126). Nebulized measles vaccines have been studied over the last decade, but Lin *et al.* (127) have developed the first live-attenuated measles dry powder vaccine that does not require reconstitution. Similarly, inhaled vaccines have been explored for measles and rubella (128), a triple combination (measles, mumps, and rubella) (129), and for protection against bioterrorism agents such as anthrax and tularaemia (130, 131). In addition, inhaled vaccines for tuberculosis (TB) are being investigated (132) and these have been reviewed by Garcia Contreras *et al.* (133) and Hokey and Misra (134).

New Therapeutics

In recent years, there has been a movement of dry powder formulations towards combination therapy, particularly for asthma and COPD (135). Combination products that are currently marketed or in clinical trials have been reviewed by Lechuga-Ballesteros *et al.* and are summarized in Table I (136). Of particular significance was the Symbicort® DPI (DPI), which contains both formoterol (a fast onset long-acting β-agonist) and budesonide (an inhaled corticosteroid). This combination dry powder has been a critical step forward, being approved for use as both a preventer and rescue therapy in Australia, Europe, and Canada. By using the same device for both daily preventative therapy and stressful rescue

Table I. Inhaled Combination Formulations for Asthma and COPD that are in Development or Commercially Available

Active ingredients	Brand	Manufacturer	Product type	Status
Fluticasone, Salmeterol	Advair®, Seretide®, Viani®, Adoair®	GlaxoSmithKline	DPI, pMDI	Market
	Seroflo®	Cipla		
Beclomethasone, Formoterol	Foster®, Formodual®, Innovair®	Chiesi	pMDI	Market
Formoterol, Mometasone	Dulera®	Merck	pMDI	Market
Budesonide, Formoterol	Symbicort®	AstraZeneca	DPI, pMDI	Market
	Foracort®	Cipla	DPI, pMDI	Market
Formoterol, Tiotropium	Duova®	Cipla	DPI, pMDI	Market
Ipratropium, Salbutamol	Combivent®	Boehringer Ingelheim	Nebulizer, Respimat®	Market
	Duoneb®	Myan	Nebulizer	Market
	Ipramol®	TEVA	DPI, Nebulizer	Market
	Duolin®	Cipla	DPI, Nebulizer, pMDI	Market
Beclomethasone, Salbutamol	Aerocort®	Cipla	DPI, pMDI	Market
Budesonide, Salbutamol	Budesal®	Cipla	Nebulizer	Market
Fenoterol, Ipratropium	Duovent®, Berodual®, Bronchodual®, Atrovent®	Boehringer Ingelheim	Nebulizer, pMDI, Respimat®	Market
	Iprateral®, Fenovent®	Cipla	Nebulizer, pMDI	Market
Ciclesonide, Formoterol, Tiotropium	Triohale®	Cipla	pMDI	Market
Formoterol, Fluticasone	Flutiform®	SkyePharma	pMDI	Market
Fluticasone, Vilanterol	Breo™	GlaxoSmithKline	DPI	Market
Glycopyrrolate, Indacaterol	Ultibro® Breezhaler®	Novartis	DPI	Market
Aclidinium, Eformoterol	LAS40464	Almirall	DPI	Filed
GSK573719, Vilanterol	–	GlaxoSmithKline	DPI	Phase III
Indacaterol, Mometasone	QMF149	Novartis	DPI	Phase III
Formoterol, Glycopyrrolate	PT003	Pearl	pMDI	Phase III
Olodaterol, Tiotropium	–	Boehringer Ingelheim	Respimat®	Phase III

Data from (136)

situations, the risk of incorrect device use by patients is minimized (137). A breath-actuated Symbicort® pMDI version was also recently introduced, giving patients an alternative inhaled dosage form (138). Similarly, inhaled tobramycin (TOBI®) is available as both tobramycin nebules and DPI as of 2013 (139). The availability of different dosage forms for the same therapy personalizes therapy to different patients to facilitate improved adherence, though this does not lead to an improvement in efficacy or patient outcome.

Dry powder aerosols have also been increasingly applied towards antibiotics for chronic, resistant infections (140-143). However, the approved dry powder antimicrobials are currently limited to tobramycin and colistimethate (Table II). In its phase III clinical trial, Colistimethate dry powder (Colobreathe DPI) was well-tolerated and demonstrated similar efficacy to the gold standard, nebulized tobramycin (142). In turn, inhaled tobramycin dry powder, formulated by PulmoSphere™ technology, was shown to provide substantially improved lung deposition, faster delivery, and more convenient administration compared to the nebulized formulation (143). Thus, it is not surprising that recent inhaled antibiotic dry powder aerosols are targeted towards diseases which are typically treated by nebulization, such as CF.

A variety of experimental antimicrobial dry powder aerosol formulations have been published (144, 145). Adi *et al.* (146) developed a spray-dried, mannitol-ciprofloxacin combination dry powder with potential to both promote mucus clearance in the respiratory tract and treat local chronic infection in diseases such as COPD and CF. Similarly, a spray-dried combination antibiotic powder containing colistin and rifampicin exhibited synergistic antibacterial activity, as well as high aerosol efficiency (FPF_{loaded}>90%) and resistance to moisture (147). Chan *et al.* (148) also reported a combination dry powder aerosol containing three first-line antitubercular drugs that could be used to treat drug-susceptible TB. A phase I pharmacokinetic study was recently conducted for an inhalable dry powder form of capreomycin, an antibiotic typically administered by injection to treat drug-resistant TB (149). A 300-mg dose was found to achieve serum concentrations above the minimum inhibitory concentration against *Mycobacterium tuberculosis*, suggesting potential for antitubercular therapy. As an alternative to antibiotics, lyophilized bacteriophages have been formulated for dry powder delivery to treat *Pseudomonas aeruginosa* (*P. aeruginosa*) infections in CF (150). A large majority of inhaled antibiotics continue to be targeted towards chronic infections such as those in CF. However, examples such as dry powder aerosols for TB indicate the emergence of inhaled antimicrobial dry powder formulations for a variety of other respiratory infections and an interest in drug combination powders.

pMDI

The challenges of pMDI formulation stability, as well as combination and new therapeutics are discussed here. Extensive discussion of pMDI formulations have been reviewed by Myrdal *et al.* (151).

Table II. Inhaled Antibiotic Formulations that are in Development or Commercially Available

Brand	Active ingredient	Manufacturer	Product type	Status
Arikace™	Amikacin	Insmed	Nebulizer	Phase III
BAY41-6551	Amikacin	Bayer Healthcare/Nektar Pharmaceuticals	Nebulizer	Phase III
Cayston®	Aztreonam	Gilead Sciences	Nebulizer	Market
-	Capreomycin	-	DPI	Phase I
-	Ciprofloxacin	Bayer Healthcare	DPI	Phase III
Pulmaquin®	Ciprofloxacin	Aradigm	Nebulizer	Phase III
Colobreathe®	Colistimethate	Forest Laboratories	DPI	Market
Promixin®	Colistimethate	Profile Pharma	Nebulizer	Market
Aeroquin®	Levofloxacin	Aptalis Pharma	Nebulizer	Phase III
TOBI®	Tobramycin	Novartis	DPI, Nebulizer	Market
Fluidosome™	Tobramycin	Axentis Pharma	Nebulizer	Market
Bramitob	Tobramycin	Chiesi Pharmaceuticals	Nebulizer	Market
AeroVanc™	Vancomycin	Savara Pharmaceuticals	DPI	Phase II

Data from (201) and (202)

Formulation Stability

For pMDI formulation development, a significant challenge is to stabilize the whole system throughout the shelf life. Unstable formulations can result in uncontrolled emitted dose and particle size, which lead to poor inhalation therapy. Drugs in pMDIs exist in solution or as particulate suspensions. While some solution formulations are susceptible to catalytic degradation in the presence of aluminum (152), many suspension formulations are affected by drug deposition on the canister and metered valve surfaces (153). These problems are partly resolved by advanced surface coating technologies (154-156). However, it is still challenging to improve stability of suspension formulations to avoid particle agglomeration, followed by creaming or sedimentation during storage.

The transition from CFC to the hydrofluoroalkane (HFA) propellants occurred more than two decades ago. However, efforts still continue on reformulating pMDI medications to use the new HFA propellants while retaining equivalent efficacy and safety profiles to their original CFC counterparts (157-161). This is due to physicochemical properties such as the vapor pressure, polarity, and densities of HFA being significantly different from those of CFC, meaning direct formulation transitions are not possible. In particular, most surfactants and excipients used in the CFC formulations are virtually insoluble in the new HFA propellants (153). This has led to the development of ethanol as a low-volatility co-solvent in HFA formulations to solubilize approved surfactants, and, more recently, to solubilize some drugs to form solution-based pMDI formulations (159-161) and eliminate issues associated with suspension stability. However, a reduction of FPF was noted for formulations with higher ethanol concentration partly due to the increased MMAD (159). Thus, the choice of optimal co-solvents for solution-based formulation still remains a challenge.

While many of the current anti-asthmatic drugs remain insoluble even with co-solvents, developing stable suspension formulations will remain a promising field to explore. Several approaches have been proposed to improve the physical stability of suspension formulations. A common approach is to use HFA soluble stabilizers, such as oligolactic acid (162), polyethylene glycol (PEG), and polyvinyl pyrrolidone (163), to minimize particle aggregation by reducing the surface energy of the drug crystals. In some cases, the polymer stabilizer (PEG) was engineered to the surface of drug microparticles (164). The approach of incorporating drugs into porous particles (an example is PulmoSpheres™) has also shown impressive improvement in the suspension stability and dose uniformity (136, 165, 166). Dellamary *et al.* (165) found that hollow particle formulations gave high FPFs (70%) and remained stable after storage under accelerated conditions (40°C/75% RH) for 3 months. They also emphasized that a wide range of drug concentrations (10 μg–1 mg) can be delivered without sacrificing the aerosolization efficiencies. Similar results are reported by Lechuga-Ballesteros and co-workers (136, 166), who incorporated drugs in spray-dried porous phospholipid particles using a cosuspension approach. They highlighted that the FPF depended solely on the porous particles because the drug concentration was many times lower (6–1,000 times). This simple formulation stabilization approach also opens the opportunities for incorporating multiple drugs of different dose into a single formulation which is discussed in the next section.

New Combination Formulations

The benefits of using more than one class of drugs to manage asthma or COPD have been evident in recent clinical research (167-169). When the diseases are not controlled with monotherapy, combined therapies of long-acting β_2 agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and/or combined inhaled corticosteroid (ICS) are recommended (170). Therefore, it is common for patients to use two or more inhalers, or combining inhaled therapy with oral medications. However, adherence to different inhaled treatments can be challenging for patients, and the total cost can be expensive. In order to realize the synergistic effect of combined therapies, significant attention placed in developing formulations that combine two or more inhalation products for delivery in a single pMDI device (136, 166, 171). This trend is reflected by the increasing number of inhalation combination formulations available commercially (172).

Challenges exist in developing combined pMDI formulations due to the different physicochemical characteristics of drugs, such as solubility and density, and the required drug doses. It is not unusual for combination formulations to have different aerosol performance when compared with the single component counterparts. Lechuga-Ballesteros *et al.* (136)

proposed a novel formulation approach by cosuspending formoterol fumarate, glycopyrrolate, and mometasone furoate microcrystals together with engineered porous phospholipid particles in HFA propellants. Single, double, and triple formulations were produced, and no significant differences in the aerosol performance were observed for individual components across the three therapies. In their later work (166), they demonstrated the drugs are irreversibly associated with the porous particles through physical adsorption.

While the development of pMDI combination formulation is progressing, interactions between drugs and the effect on formulation stability and aerosol performance may be of concern. Rogueda *et al.* (25) investigated the drug-drug interaction of the two marketed pMDI formulations, Symbicort® (AZ; budesonide and formoterol fumarate, 160/4.5 μg) and Seretide®/Advair® (GSK; salmeterol xinafoate and fluticasone propionate, 250/25 μg). They suggested the stronger drug-drug interaction found in salmeterol and fluticasone may lead to heteroflocculation, increase aerosol particle size, and, consequently, affect the aerosolization efficiency. Nonetheless, adapting stabilization approaches developed for single drug formations may offer guidance towards methods to minimize the adverse effects brought by drug-drug interactions in combination formulations.

New Therapeutics

Recently, pulmonary administration has become an attractive delivery route for systemically acting drugs because it is noninvasive, avoids first-pass metabolism, and the large lung surface area and thin alveolar epithelium allows fast drug absorption. The localized delivery of protein, peptide, and gene therapy for lung diseases has been explored (173-176). Though most efforts have been placed on developing dry powder or nebulized formulations to deliver these new therapeutics, the convenience and cost advantages of pMDIs may eventually lead to their use in the delivery of these therapies.

Various studies have looked at stabilizing proteins and genes in the HFA propellants, which has been a major concern for the development of such formulations. Li and Seveille (174) demonstrated co-spray-dried BSA with sodium carboxymethylcellulose can help protect protein integrity and the resulting powders could be formulated with the HFA propellant to give good aerosolization performance (FPF≥50%). Tan *et al.* (173) proposed another approach to preserve the bioactivity of protein for pMDI formulations. A lysozyme solution was freeze-dried using a co-solvent of water/tert-butyl alcohol in the presence of lecithin and lactose as the surfactant and cryoprotectant, respectively, to form protein nanoparticles. The retention of lysozyme bioactivity in the HFA formulations was reported to be up to 98%. Bains *et al.* (175) demonstrated that surfactant-coated pDNA nanoparticles can be incorporated into a HFA propellant and the resulting formulation was aerosolizable with the biological functionality of the pDNA retained. While development of pMDI formulations to deliver new therapeutics for systematic and local diseases is still in the infancy stage, these studies demonstrated its viability.

Nebulizers

Understanding Formulation Parameters

A key challenge in formulating nebulizer therapeutics is in understanding the effect of key formulation parameters such as viscosity, surface tension, and electrolyte concentration on droplet aerosol properties. For example lung deposition, particularly in the peripheral airways, is influenced by hygroscopic properties of nebulized aerosols. Interestingly, Haddrell *et al.* (177) found that the droplet size of nebulized aerosols can be greatly reduced with micromolar concentrations of larger Pluronic polymers added to the formulations. For newer vibrating mesh nebulizers, viscosity and conductivity are particularly important. Specifically, an increase in both these parameters reduced aerodynamic size, while increased electrolyte concentrations enhanced aerosol output (178, 179). Although some parameters are well-understood, greater understanding is still needed regarding other factors such as how the behavior of non-Newtonian fluids influences nebulizer droplet formation (180).

In addition, the effect of these variables depends on the nebulizer type. Najlah *et al.* (181) recently investigated the effect of suspension particle size on nebulized aerosol properties using a latex microsphere model suspension. Aerosol characteristics were generally unaffected by suspension particle size (1–10 μm) for jet nebulizers. In contrast, for ultrasonic and vibrating mesh nebulizers, increasing suspension particle sizes up to 10 μm enhanced aerosol output and FPF. The choice of formulation excipients such as phospholipids can also have a profound effect on final aerosol droplet size (180). In testing the aerosol performance of a liposomal amphotericin B formulation with three jet nebulizers, Lambros *et al.* (182) found that while the output rate increased with higher drug concentration regardless of device, particle size distributions varied considerably. These studies highlight the need to couple nebulizer formulations with specific nebulizers to ensure consistent clinical efficacy. Further investigations are necessary to improve the ability to tailor nebulized aerosol lung delivery, particularly for newer nebulizer types.

Drug Encapsulation

Drug encapsulation has been popular for nebulized therapies to extend drug release, encapsulate hydrophobic drugs, and to target delivery, for example, to alveolar macrophages. In particular, there has been a recent focus on liposomes and their optimization. The concept of liposomal "phase transition release" has recently been proposed to control pulmonary drug release rate from nebulized liposomes, whereby adjustment of the phase transitions of liposomes above body temperature directly increased pulmonary drug retention in an *ex vivo* lung model (183). Using nebulized liposomal ciprofloxacin, another study demonstrated that *in vivo* liposomal pharmacokinetic behavior can be predicted from a combination of data from *in vitro* membrane diffusion and cell models and *ex vivo* perfused lung methods (184). A unique formulation of ciprofloxacin, which contained both immediate and sustained-release (liposomal) ciprofloxacin, was shown to retain its integrity in response to nebulization (185). Finally,

Gaspar *et al.* (186) demonstrated that vibrating mesh nebulizers (Aeroneb Pro and Aeroprobe) are particularly suited for delivery of liposomal formulations with rapid delivery times and high retention of liposome structural integrity. Remarkable liposomal stability using this class of nebulizers was also reported by Beck-Broichsitter *et al.* (183). Liposomes for nebulized delivery is extensively reviewed by Cipolla *et al.* (187).

The antifungal agent amphotericin B, which has well-established toxic systemic side effects, is a prime example of an encapsulated drug formulation for nebulization. Alexander *et al.* (188) took an interesting approach by skipping the reformulation step and directly nebulizing a commercially available liposomal amphotericin B formulation approved for intravenous infusion (Ambisome™). Excellent fine particle fractions (80–90%) and maintenance of liposomal integrity was demonstrated by *in vitro* testing with four different jet nebulizers. Albasarah *et al.* also presented a liposomal formulation but coated with chitosan to extend contact time with the mucosal tissue. Coupling with a jet nebulizer resulted in a good fine particle fraction (60%) and antifungal activity against *Candida albicans* and *Candida tropicalis*. They also found that an ethanol-based proliposome method was found superior to other tested manufacturing methods and found to have greatest drug loading (80%). In addressing safety concerns, a clinical study in lung transplant patients found that prophylactic nebulized liposomal amphotericin B did not alter lipid content pulmonary surfactant (189). Alternatively, Alssadi *et al.* proposed encapsulating amophotericin B in non-ionic surfactant vesicles for nebulized delivery. In rat models of infection, these proved effective in reducing fungal lung burdens of invasive pulmonary aspergillosis but also demonstrated systemic efficacy by suppressing *Leishmania donovani* liver parasite load. Plasma concentrations were considerably lower compared to unencapsulated amphotericin B, suggesting reduced systemic toxicity. Thus, recent work with encapsulated amphotericin B/antifungals is a promising example of extended release nebulized formulations that achieve high target concentrations while limiting unwanted side effects.

New Therapeutics

Nebulizer formulations have been trialed in a number of novel applications. For example, the formulation of siRNA-encapsulated cross-linked chitosan nanoparticles may have potential for treatment of both infectious and inheritable disease (190). Nebulized sildenfil has also been investigated (191, 192) as aerosolized phosphodiesterase type 5 inhibitors may offer potential benefits in the treatment of CF by restoring ion transport (193). Recently, a large number of reported nebulizer formulations have focused on infectious diseases and cancer.

The efficacy and benefits of inhaled antibiotic formulations are well-established, and we continue to see reformulation of systemic antibiotics for inhaled administration (Table II). Nebulized gentamicin has demonstrated efficacy in non-CF bronchiectasis against chronic colonization by *P. aeruginosa*, with twice-daily 80-mg dose leading to a reduction of bacterial load that may decrease the number of exacerbations as well as the risk of re-infection (194). Similarly, nebulized dual release ciprofloxacin (Pulmaquin) has demonstrated both antipseudomonal activity and efficacy with respect to time to first exacerbation in a phase II trial of non-CF bronchiectasis patients (195). For CF-associated pseudomonal infection, nebulized aztreonam has shown efficacy in phase III clinical trials in reducing *P. aeruginosa* density in sputum and prolonging time between doses, and is now available in specialty pharmacies (196). Cooper *et al.* (197) suggested a different treatment strategy to antibiotics, by pulmonary delivery of bacteriophages active against *P. aeruginosa*. While these have shown satisfactory *in vitro* performance and stability, the nebulized formulation still needs refinement of endotoxin levels to meet regulatory standards. Finally, Manca *et al.* (198) developed a nebulized suspension of isoniazid-gelatin conjugate microparticles containing rifampicin, which reduced toxicity to A549 alveolar epithelial cells compared to a rifampicin solution. This demonstrated that the use of nebulized antibiotics for diseases not conventionally treated by nebulization.

Nebulized therapy has also been suggested for treatment of cancer, particularly with repurposed drugs. Nanostructured lipid carrier nanoparticles were used to encapsulate celecoxib, a lipophilic inhibitor of the cyclooxygenase-2 enzyme with potential anticancer activity (199). Nebulization of the nanoparticle suspension was found to improve pulmonary bioavailability of celecoxib compared to a solution formulation. Coenzyme Q_{10} (CoQ_{10}) may act against melanoma and other malignancies. Carvalho *et al.* (180) used microfluidization to formulate a phospholipid-stabilized aqueous dispersion of submicron CoQ_{10} particles. While shown suitable for delivery by a vibrating mesh nebulizer *in vitro*, *in vivo* efficacy remains to be demonstrated. The drug 5-azacytidine has demonstrated activity against non-small-cell lung cancer in phase II trials (200). Jet-nebulized 5-azacytidine to nude rats with engrafted lung tumors demonstrated major increases in drug lung tissue half-life compared to intraperitoneal delivery and significant reductions in lung tumor burden (200). Recent nebulization of anticancer therapy has thus demonstrated unique formulation techniques for hydrophobic drugs such as celecoxib and CoQ_{10} in an aqueous medium, as well as evidence for potential efficacy.

FUTURE DIRECTIONS AND CONCLUSIONS

The recent advances in inhaled devices and formulations indicate certain trends in the field. High-dose dry powder alternatives to nebulized formulations are increasingly popular and will be facilitated by development of newer variants of high dose (>100 mg) DPIs. Single-use disposable dry powder inhalers will be coupled with applications in the nascent field of inhaled vaccines, as well as for infectious diseases to disease transmission. Dose counters and breath-actuated MDIs are anticipated to improve asthma control. Nebulizers, particularly software-aided systems such as the AKITA® which can accurately direct lung deposition and total dosing, will play a crucial role in novel cancer therapies and improving reliability of clinical trials on inhaled therapeutics. It is also anticipated that a greater proportion of future aerosol formulations will involve repurposed drugs. While the global proliferation of electronic technology has seen increased integration of guidance software and digital logging systems in different inhaler

devices, its impact on patient behavior and clinical efficacy will be an interesting field to watch.

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