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Review Article

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Delivery Technologies for Orally Inhaled Products: an Update

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Abstract. Orally inhaled products have well-known benefits. They allow for effective local administration of many drugs for the treatment of pulmonary disease, and they allow for rapid absorption and avoidance of first-pass metabolism of several systemically acting drugs. Several challenges remain, however, such as dosing limitations, low and variable deposition of the drug in the lungs, and high drug deposition in the oropharynx region. These challenges have stimulated the development of new delivery technologies. Both formulation improvements and new device technologies have been developed through an improved understanding of the mechanisms of aerosolization and lung deposition. These new advancements in formulations have enabled improved aerosolization by controlling particle properties such as density, size, shape, and surface energy. New device technologies emerging in the marketplace focus on minimizing patient errors, expanding the range of inhaled drugs, improving delivery efficiency, increasing dose consistency and dosage levels, and simplifying device operation. Many of these new technologies have the potential to improve patient compliance. This article reviews how new delivery technologies in the form of new formulations and new devices enhance orally inhaled products.

KEY WORDS: orally inhaled product; inhalation; delivery technology; smart inhaler; dry powder inhaler.

INTRODUCTION

The benefits of *orally inhaled products* (OIPs) have been widely reported. These benefits include effective local administration of drugs that treat pulmonary diseases and rapid absorption and avoidance of first-pass metabolism for systemically acting drugs (1). However, several problems remain unsolved. These problems include dosing limitations (2–4), inefficient and variable lung deposition of the drug (5–7), and high drug deposition in the oropharynx region (5,7). Moreover, difficulties in oral aerosol delivery can be amplified by intrapatient variability and interpatient heterogeneity. If the device or formulation is susceptible to variations in inhalation effort, improper or inconsistent dosing techniques can significantly affect the pulmonary dose delivered for a single patient. Similarly, differences in age (8), respiratory health (9), and training (10) between patient groups can greatly impact therapeutic performance.

Historically speaking, early development of inhaled products was focused on the treatment of asthma with monotherapy (11), *i.e.*, with only a single drug substance included in the formulation. Since 2010, about one half of the newly approved OIPs for asthma or *chronic obstructive pulmonary disease* (COPD) are fixed-dose combinations that deliver two or three drug substances simultaneously to enhance therapeutic efficacy (see Table I). Also, the therapeutic indications for drugs administered to the lungs continue to expand from localized pulmonary diseases to systemic indications, including diabetes (13), measles (14), Parkinson's disease (15,16), schizophrenia (17), and influenza (18,19) among others. As the indications for inhalation therapy expand, improved control of dosing uniformity and product quality attributes will be warranted. Delivery technologies are now able to address, at least partially, many of the historical problems encountered with inhaled drug products, and promising improvements in patient compliance and drug efficacy have been reported recently (20–22).

In this review, we discuss examples of recent technology advancements in orally inhaled products, and we analyze their advantages and limitations based on the current available literature. Technology advancements related to formulation and device technologies are reviewed, focusing on formulation factors related to the engineering of particle density, size, and shape, as well as modifications in surface energy. In terms of device technologies, we focus on the type of device and its delivery technology, including *smart inhalers*, *dry powder inhalers* (DPIs), *nebulizers*, *soft mist inhalers*, and

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Table I. Examples of FDA-Approved OIPs Between 1996 and 2017 (12)

Year approved by FDA	Type	Name	Use	Active pharmaceutical ingredient(s)	Inactive ingredient(s)
2017	DPI	Trelegy Ellipta	COPD	Fluticasone furoate/umeclidinium bromide/vilanterol trifenatate	Lactose monohydrate, magnesium stearate
		Airduo Respiclick	Asthma	Fluticasone propionate/salmeterol xinafoate	Lactose monohydrate
		Armonair Respiclick	Asthma	Fluticasone propionate	Lactose monohydrate
	pMDI	QVAR Redihaler	Asthma	Beclomethasone dipropionate	HFA-134a, ethanol
2016	pMDI	Bevespi Aerosphere	COPD	Formoterol fumarate/glycopyrrolate	HFA-134a, porous particles (comprised of 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride)
2015	DPI	Proair Respiclick	Bronchospasm	Albuterol sulfate	Lactose monohydrate
		Utibron Neohaler	COPD	Glycopyrrolate/indacaterol maleate	Lactose monohydrate, magnesium stearate
	Soft mist	Stiolto Respimat	COPD	Olodaterol hydrochloride/tiotropium bromide	Water, benzalkonium chloride, edetate disodium, hydrochloric acid
2014	DPI	Arnuity Ellipta	Asthma	Fluticasone furoate	Lactose monohydrate
		Incruse Ellipta	COPD	Umeclidinium bromide	Lactose monohydrate, magnesium stearate
	pMDI	Asmanex HFA	Asthma	Mometasone furoate	HFA-227, ethanol, oleic acid
	Soft mist	Spiriva Respimat	COPD/asthma	Tiotropium bromide	Water, benzalkonium chloride, edetate disodium, hydrochloric acid
		Striverdi Respimat	COPD	Olodaterol hydrochloride	Water, benzalkonium chloride, edetate disodium, anhydrous citric acid
2013	DPI	Anoro Ellipta	COPD	Umeclidinium bromide/vilanterol trifenatate	Lactose monohydrate, magnesium stearate
		Breo Ellipta	COPD	Fluticasone furoate/vilanterol trifenatate	Lactose monohydrate, magnesium stearate
		TOBI Podhaler	Cystic fibrosis	Tobramycin	1,2-Distearoyl-sn-glycero-3-phosphocholine, calcium chloride, sulfuric acid
2012	DPI	Tudorza Pressair	COPD	Aclidinium bromide	Lactose monohydrate
2011	DPI	Arcapta Neohaler	COPD	Indacaterol maleate	Lactose monohydrate
	Soft mist	Combivent Respimat	COPD	Albuterol sulfate/ipratropium bromide	Water, benzalkonium chloride, edetate disodium, hydrochloric acid
2010	pMDI	Dulera	Asthma	Formoterol fumarate/mometasone furoate	HFA-227, anhydrous alcohol, oleic acid
	Nebulizer	Cayston	Cystic fibrosis	Aztreonam	Sodium chloride, water
2009	Nebulizer	Tyvaso	Pulmonary arterial hypertension	Treprostinil	Sodium chloride, sodium citrate, sodium hydroxide, hydrochloric acid, water
2008	pMDI	Alvesco	Asthma	Ciclesonide	HFA-134a, Ethanol
2007	Nebulizer	Perforomist	COPD	Formoterol fumarate	Water, sodium chloride, citric acid, sodium citrate
2006	DPI	Foradil Certihaler	Asthma/bronchospasm	Formoterol fumarate	Lactose monohydrate, magnesium stearate
		Pulmicort Flexhaler	Asthma	Budesonide	Lactose
	pMDI	Advair HFA	Asthma	Fluticasone propionate/salmeterol xinafoate	HFA-134a
		Aerospan HFA	Asthma	Flunisolide	HFA-134a, ethanol
		Symbicort	Asthma/COPD	Budesonide/formoterol fumarate dihydrate	HFA-227, Povidone K25, Polyethylene glycol 1000 NF
	Nebulizer	Brovana	COPD	Arformoterol tartrate	Isotonic saline solution, citric acid, sodium citrate
2005	DPI	Asmanex Twisthaler	Asthma	Mometasone furoate	Anhydrous lactose
	pMDI	Xopenex HFA	Bronchospasm	Levalbuterol tartrate	HFA-134a, dehydrated alcohol, oleic acid
2004	DPI	Spiriva Handihaler	COPD	Tiotropium bromide	Lactose monohydrate
	pMDI	Atrovent HFA	COPD	Ipratropium bromide	HFA-134a, water, dehydrated alcohol, anhydrous citric acid
		Flovent HFA	Asthma	Fluticasone propionate	HFA-134a
		Proair HFA	Bronchospasm	Albuterol sulfate	HFA-134a, ethanol
2001	DPI	Foradil Aerolizer	COPD/asthma/ bronchospasm	Formoterol fumarate	Lactose
	pMDI	Ventolin HFA	Bronchospasm	Albuterol sulfate	HFA-134a
	Nebulizer	Duoneb	COPD	Albuterol sulfate/ipratropium bromide	Isotonic water, sodium chloride, hydrochloric acid, edetate sodium
2000	DPI	Advair Diskus	Asthma/COPD	Fluticasone propionate/salmeterol xinafoate	Lactose monohydrate
		Flovent Diskus	Asthma	Fluticasone propionate	Lactose monohydrate
	pMDI	QVAR	Asthma	Beclomethasone dipropionate	HFA-134a, ethanol
	Nebulizer	Pulmicort Respules	Asthma	Budesonide	

Table I. (continued)

Year approved by FDA	Type	Name	Use	Active pharmaceutical ingredient(s)	Inactive ingredient(s)
					Disodium edetate, sodium chloride, sodium citrate, citric acid, Polysorbate 80, water
1999	Nebulizer	Xopenex	Bronchospasm	Levalbuterol hydrochloride	Sodium chloride, sulfuric acid, water
1997	DPI	Flovent Rotadisk	Asthma	Fluticasone propionate	Lactose
		Pulmicort Turbuhaler	Asthma	Budesonide	none
		Serevent Diskus	Asthma/bronchospasm/ COPD	Salmeterol xinafoate	Lactose monohydrate
	Nebulizer	TOBI	Cystic fibrosis	Tobramycin	Water, sodium chloride
1996	pMDI	Flovent	Asthma	Fluticasone propionate	Trichlorofluoromethane, dichlorodifluoromethane
		Proventil HFA	Bronchospasm	Albuterol sulfate	HFA-134a, ethanol, oleic acid

DPI dry powder inhaler, *COPD* chronic obstructive pulmonary disease, *PMDI* pressurized metered dose inhaler

pressurized metered dose inhalers (pMDIs). Many of these new technologies have made progress toward improving dose consistency, dose amounts, device portability, convenience of use, and efficiency of delivery, which results in improved patient outcomes.

FORMULATION TECHNOLOGY

For inhaled drug products, the aerodynamic particle size of the drug is the key parameter that affects regional lung deposition (23). The aerodynamic diameter (d_a) is given by Eq. (1) (24):

$$d_a = d_e\sqrt{\frac{\rho}{\rho_0\chi}} \quad (1)$$

where d_e is the equivalent volume diameter, ρ is the spherical particle density, ρ_0 is the unit density, and χ is the dynamic shape factor (23,24).

In order to effectively achieve lung deposition, it is generally accepted that the aerodynamic diameter of inhaled particles must be 1–5 μm (25), while the aerosol dose less than 3 μm showed a strong correlation with whole lung deposition (26). Therefore, at least from a particle engineering standpoint, the three main factors that can determine aerodynamic diameter are *particle density*, *particle size* (*i.e.*, diameter), and *dynamic shape factor*. Lower particle density and smaller geometric size lead to a smaller aerodynamic diameter and change the interparticulate forces that increase the probability that a particle is deposited in the deep lung. Also, the dynamic shape factor plays an important role in delivering particles to the lung (27). A needle-shaped particle has a higher shape factor than a spherical particle, leading to a smaller aerodynamic diameter (27). However, this needle-shaped particle may also significantly affect the particle–particle contact area. As a result, interparticulate forces are increased, which leads to a poorly dispersing powder (27). In addition to these three factors, the aerosol performance of a dry powder formulation is affected by surface energy of either the carrier, the drug(s), or both, which can be modified by the alteration of surface roughness or by the addition of dispersion-enhancing excipients (28–30). Therefore, the improvement of the aerosol performance of inhaled drug products using powder and particle engineering approaches has been achieved primarily by controlling particle density, size, shape, and surface energy, which are discussed in more detail below.

Particle Density

Based on Eq. (1), the low density of particles reduces their aerodynamic particle size, resulting in a particle aerodynamic diameter that is smaller than its geometric diameter. PulmoSphere® is a technology capable of producing low-density particles by manufacturing a high-surface area, sponge-like particle morphology. A perfluorooctyl bromide-in-water emulsion containing distearoyl phosphatidylcholine (DSPC) and calcium chloride (2:1 mol/mol) (31) as the primary excipients is processed by spray-drying to produce phospholipid-based small, porous PulmoSphere® particles with a tapped density of 0.01–0.50 g/cm^3 (32) (Fig. 1a). Three different formats are applicable to PulmoSphere® formulations, based on different types of feedstock for spray-drying: *solution-based*, *suspension-based*, and *carrier-based* formulations (32).

The preparation process for solution-based PulmoSphere® involves the following steps: The continuous phase of oil-in-water feedstock with fully dissolved drug substance is spray-dried rapidly on the milliseconds scale (36–39). While the fast-diffusing drug substance becomes amorphous and is distributed throughout the droplet during fast drying, the slow-diffusing excipients are concentrated at the surface interface (32). For the product TOBI® Podhaler®, which is based on PulmoSphere® technology, a total of 14% *w*/*w* of DSPC is used in the formulation, but the particle surface is composed of over 90% *w*/*w* DSPC (40). By controlling the volume fraction of the oil phase in the feedstock, particle properties (*e.g.*, geometric diameter, surface area, tapped density, porosity) can be controlled (41). The TOBI® Podhaler®, the first FDA-approved product manufactured using the solution-based PulmoSphere® technology, is the second tobramycin inhalation formulation marketed by the Novartis Pharmaceuticals Corporation. A recent stability study by Miller *et al.* shows that the glassy particles of TOBI Podhaler are physicochemically stable, and aerosol performance is maintained after exposure of packaged product to either 25°C/60% RH or 30°C/75% RH for at least 3 years (42).

Alternatively, unlike the dissolved drug substance in the solution-based PulmoSphere®, in the suspension-based PulmoSphere® technology, the drug substance is

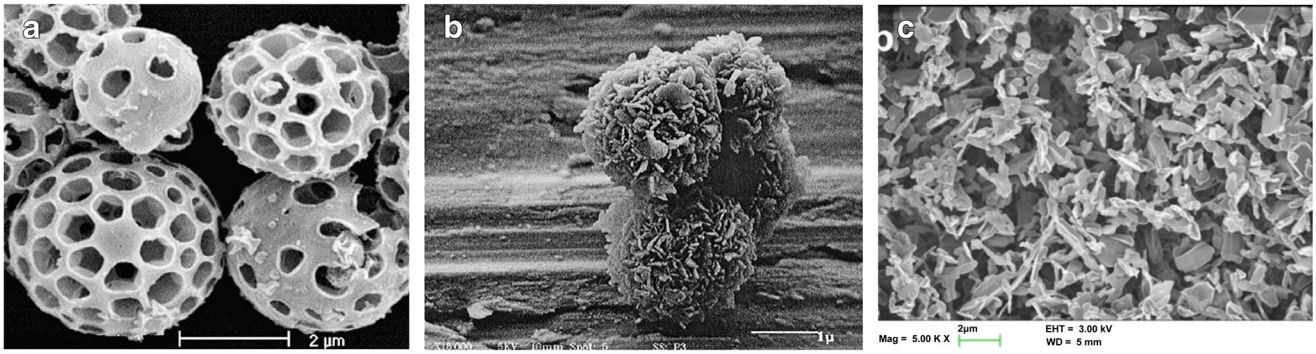

Fig. 1. SEM images of engineered low-density particles. **a** PulmoSphere® solid foam particles (33). Copyright © Springer Science+Business Media, LLC 2007. **b** Four Technospheres® loaded with insulin (18% *w*/*w*) intended for pulmonary administration (34). Reproduced with permission from Respiratory Drug Delivery, Virginia Commonwealth University and RDD Online. **c** TFF particle of voriconazole (35). Reproduced with permission from Elsevier

incorporated as fine particles in a feedstock suspension (33,39,43,44). Either crystalline or amorphous drug particles are coated with PulmoSphere® excipients, producing single particles (32). The mass median diameter of the drug particles in the suspension feedstock should be less than 2 µm, and 90% of these particles are required to be less than 5 µm in order to effectively coat the drug substance with the PulmoSphere® shell (45). Ciprofloxacin dry powder for inhalation was developed by Bayer Healthcare Pharmaceuticals, Inc. using this suspension-based format (46–48).

A carrier-based format can produce micronized drug particles that strongly adhere to the small porous PulmoSphere® particles as respirable agglomerates (32,49,50). Since the agglomerates are delivered into the lungs in this PulmoSphere® format, the adhesive forces between the drug and carrier and the cohesive forces between drug particles are less correlated with the aerosol performance of the bulk powder (32). The carrier-based PulmoSphere® format is produced in two steps: first, the manufacture of the PulmoSphere® carrier and co-suspension of micronized drug substance with the carrier in a nonsolvent (32). This nonsolvent can be removed by spray-drying (51). Due to the usage of a nonsolvent other than water, this format of PulmoSphere® may be well suited for physically or chemically unstable formulations in water (32,51). This format also increases the physical stability of potent crystalline drug substances by maintaining their crystallinity during the manufacturing process (32).

In 2016, the FDA approved Bevespi Aerosphere®, by AstraZeneca Pharmaceuticals LP. It is manufactured using the carrier-based PulmoSphere® format (52). Bevespi Aerosphere is a fixed-dose combination of glycopyrrolate, a *long-acting muscarinic antagonist* (LAMA), and formoterol fumarate, a *long-acting beta$_2$-adrenergic agonist* (LABA) (53). The recent study by Taylor *et al*. showed that a fixed-dose combination of glycopyrrolate and formoterol fumarate (18/9.6 µg), which was manufactured by the same technique of Bevespi Aerosphere® with double the amount of drugs, was efficiently deposited in all regions of the lungs with low exhaled fraction (54).

One difficulty of delivering fixed-dose suspension combinations of drugs using a pMDI is maintaining a uniform aerosol performance of the actives (55,56). For instance, Advair® HFA has a fine particle fraction (FPF) of 48–52% for fluticasone propionate in the three different doses of fluticasone (44 to 220 µg/actuation) while 63–75% for a fixed dose of salmeterol xinafoate (57). The co-suspension of porous particles using the carrier-based PulmoSphere® format promotes uniform dosing of pMDIs, presenting consistent drug distributions (58). Furthermore, Martinez *et al*. performed two phase III trials and confirmed that the glycopyrrolate/formoterol formulation using the carrier-based PulmoSphere® format exhibited better efficiency than the individual monodose bronchodilator formulations in patients with moderate-to-very severe COPD, with a significantly lower use of rescue medications during the study periods (59).

While PulmoSphere® particles are produced by spray-drying, freeze-drying technology is also applicable in producing particles with low density. Technosphere® is another technology used to produce a large surface area and high internal porosity, resulting in low-density powder (60) (Fig. 1b). Afrezza®, the second inhaled insulin marketed product, is manufactured using Technosphere® technology (61). Fumaryl diketopiperazine (FDKP) is used as a primary ingredient for Technosphere® formulations of inhaled insulin. FDKP crystalline nanoparticles prepared by a controlled, pH-induced crystallization process self-assemble into 3D spheres that can capture insulin inside the spheres (62). The dry particles of Afrezza® present a mass median aerodynamic diameter (MMAD) of about 2.5 µm with an internal porosity of 70% (63).

Thin film freezing (TFF) cryogenic technology is also used to manufacture low-density particles. With freezing rates up to 10^4 K/s (64), TFF can produce nanostructured particles with high surface area and low bulk density (65) (Fig. 1c). Beinborn *et al.* reported producing amorphous voriconazole for DPI delivery containing voriconazole and polyvinylpyrrolidone K25 (1:3 *w*/*w*) with 43 m^2/g of specific surface area and 0.013 g/cm^3 of bulk density (35). Watts *et al.* also reported respirable low-density tacrolimus formulations produced by TFF, and they reported densities less than 0.01 g/cm^3, while the FPFs were as high as 69% when tested with 3 mg of powder in the Handihaler® at a flow rate of 51 L/min (4 kPa) (66).

Particle Size

Typically, when a drug is delivered to the pulmonary pathways, a significant amount is lost because of drug deposition in the oropharynx or mouth regions (67) due to

inertial impaction of large particles or particles that were insufficiently deaggregated (23). The AERx® pulmonary drug delivery system, which was first introduced in the 1990s, can generate small aerosols, less than 3 μm, to avoid the drug deposition in the oropharynx and more central airways, and efficiently deposit drugs with an insignificant exhaled fraction by hygroscopic particle growth (68,69). More recently, Longest *et al*. suggested a novel approach to control the growth of nanoparticles to the micron size range to overcome the loss of the drug deposited in the oropharynx or mouth regions (70–73). Spray-dried nanoparticles can bypass deposition in the oropharynx and mouth regions, but when delivered with saturated or supersaturated warm air, their size increases in the airways due to the condensation of warm water vapor on the particles (74). This method is called *enhanced condensational growth* (ECG) (74). The increased particle size is within the range of 2–3 μm (74).

Similarly, prior research has described the use of a hygroscopic excipient (*e.g.*, mannitol, citric acid, sodium chloride) to increase the particle size by stronger interaction with relative humidity of the airways, causing growth by condensation without an external source of water vapor (73). Because the initial size of the particles is submicron (75), only slight deposition is expected in the mouth–throat region (76). The particle size increases significantly after the aerosol reaches into the deep lung. This method, which uses an excipient, is called *enhanced excipient growth* (EEG) (75). Using EEG, the particle diameter growth ratio was measured up to 4.6 times the original size, and this growth occurred with both hygroscopic and nonhygroscopic drugs when the excipient mass loadings were 50% and below (73). Son *et al*. reported that, using EEG, the performance of spray-dried albuterol sulfate, with mannitol as a hygroscopic excipient along with L-leucine and poloxamer 188, not used as excipients in approved formulations yet, exhibited a 4.1% mouth–throat deposition using a realistic mouth–throat model (77). EEG formulations were recently tested on low-air volume in-line DPIs to deliver high-dose pharmaceutical aerosols during mechanical ventilation (78,79).

Particle Shape

Particle shape is another factor that influences aerodynamic particle size. Needle-shaped particles can reduce aerodynamic size, based on Eq. (1), due to larger value of χ. Thus, they can achieve improved aerosol performance and delivery of the drug into the deep lung area. Additionally, elongated particles have a greater chance of avoiding macrophage clearance by phagocytosis when deposited with their long axis (23). Using elongated particles is beneficial, but it is difficult to achieve the fabrication of nonspherical particles with reproducibly controlled dimensions.

Liquidia Technologies has developed a novel particle manufacturing technology to fabricate particles using a proprietary roll-to-roll manufacture (80) (see Fig. 2). *Particle replication in nonwetting templates* (PRINT®) is a unique technology that can make particles with a specific size, shape, and composition (82). PRINT® technology can support drug development for diverse drug substances, including small molecules, biologics, single agents, fixed-dose combinations, and vaccines (84).

Mack *et al*. tested the aerosol properties of treprostinil dry powder for inhalation, made using PRINT® technology (83). The aerodynamic diameter of triangular treprostinil particles was measured as 1.6–1.7 μm, and the FPF was around 90% when tested with 10 mg of PRINT particles loaded in a low-resistance monodose DPI (Plastiape; Lecco, Italy) at a flow rate of 90 L/min (4 kPa). In a stability study of a PRINT–treprostinil formulation under accelerated conditions (40°C at 75% relative humidity), FPF was maintained at 90% for 12 weeks (83).

This precise particle design using PRINT® technology allows for the scalable manufacturing of inhalable pharmaceutical particles that are available in a nearly unlimited number of particle shapes and sizes, with a size range from nanoscale to micron-scale (81,82). PRINT technology can be a useful solution for inhaled drug product development, which has difficulty fabricating particle shapes to achieve suitable aerodynamic properties by changing the dynamic shape factor χ in Eq. (1).

Surface Energy

The earlier generation of DPI products was limited to milling large bulk powders into smaller particles, then mixing a micronized drug with a carrier, usually lactose (85). By this process, the contact area of particles affects the aerosol performance of a dry powder, and the shear stress (aerosolization forces) should be higher than the adhesion forces between the particles (86). As the highest surface energy is found on the flat, smooth, and clean surfaces of materials, greater surface roughness can reduce surface energy, reducing particle contact area, thus increasing distance between particles (86) to enhance particle dispersion.

Granulated lactose, recently evaluated by Du *et al*., demonstrates the relationship between surface roughness and aerosol performance (85,87,88). A large size fraction of granulated lactose exhibited a rougher surface. Therefore, the large size fraction had lower surface energy and presented better aerosol performance than the smaller size fraction that had smoother surfaces. Du *et al*. find no significant effect on solid-state properties, specific surface area, true density, and flowability with different sizes of granulated lactose; however, roughness of surface, bulk, and tapped densities were different based on the size of the granules (88). Whereas carrier-based DPI formulations commonly have low drug loading, granulated lactose presents promising results for high drug loading. In the case of salbutamol sulfate, higher drug loading (30%) exhibited better aerosol performance with a larger fraction of granulated lactose at a higher flow rate, while aerosol performance and flow rate were independent from drug loading in the case of rifampicin (87). Therefore, with high drug loading capability, granulated lactose can be useful for designing and optimizing DPI formulations with high drug loading for improved aerosol performance and flow rate independence (87).

Using a dispersion-enhancing excipient without lactose or another carrier has been reported to reduce surface energy. Sou *et al*. suggest that the hydrophobicity of leucine causes its migration to the surface of droplets during spray-drying, thus modifying the surface energy of the particles (89). The use of leucine as an aerosolization enhancer

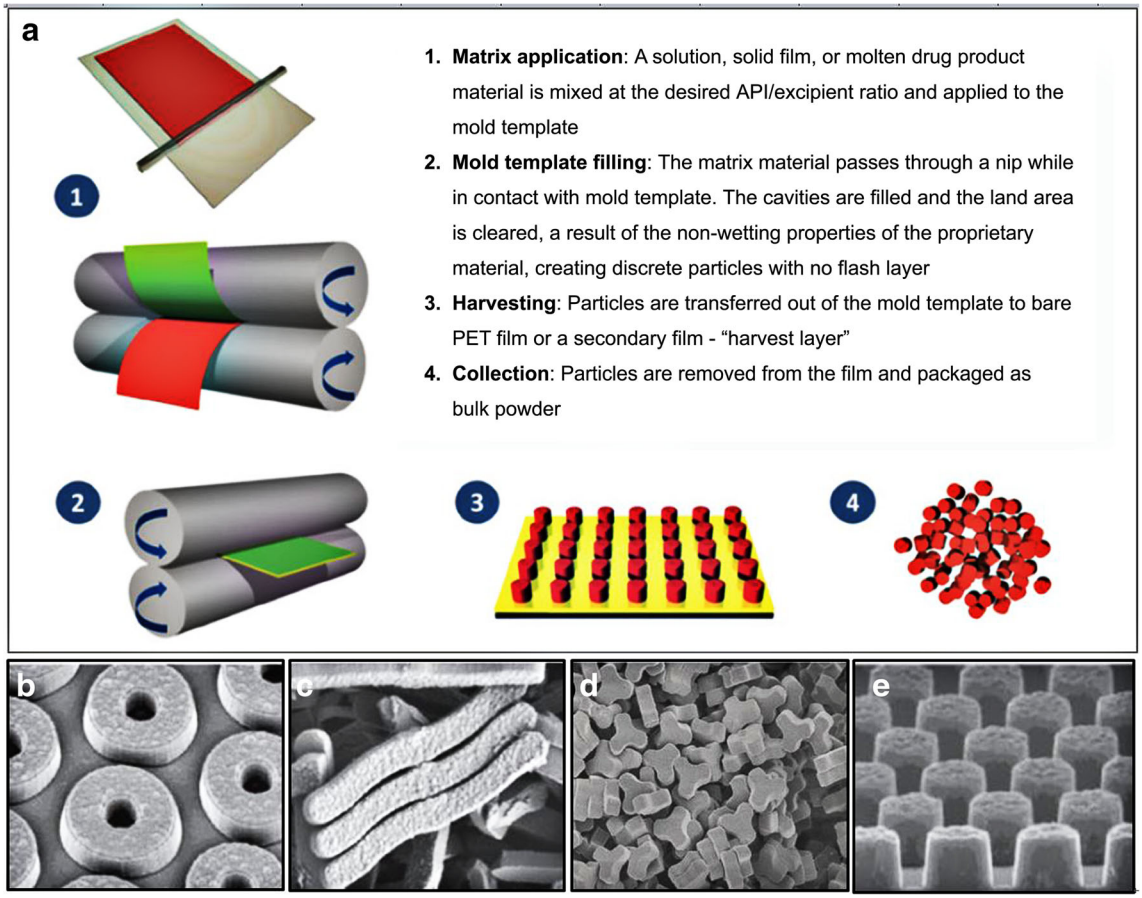

Fig. 2. **a** Sequential steps of the PRINT particle manufacturing process (81). **b** Three-micrometer fenestrated "torus particles" (82). **c** Rod-like particles (82). **d** Micrograph of PRINT–treprostinil particles (83). **e** One-micrometer cylinders (82). Reproduced with permission from Respiratory Drug Delivery, Virginia Commonwealth University and RDD Online

successfully demonstrates that surface-modified salbutamol sulfate was suitable for delivery by inhalation without a carrier when reasonable surface roughness was achieved (86).

More recently, AeroVanc™ (90–92), a vancomycin DPI formulation, and meloxicam DPI formulation (93) have been developed to include leucine as an excipient. In addition, Pulmatrix, Inc. has developed a levofloxacin DPI formulation containing leucine and sodium chloride without lactose using iSPERSE™ (*inhaled small particles easily respirable and emitted*) technology (94), which is applicable not only to small molecule drugs, but also to large molecules such as immunoglobulin G (95,96).

Magnesium stearate has also been claimed to reduce surface energy and powder cohesion, thus improving aerosol performance due to its high hydrophobicity (97). In the studies by Zhou *et al.*, adding just 1% *w/w* magnesium stearate to formulations produced by jet-milling (which include salbutamol sulfate, salmeterol xinafoate, and triamcinolone acetonide) exhibited increased FPF by at least 14–22%, with a significant decrease in surface cohesion (98,99).

DEVICE TECHNOLOGIES

Devices are integral to achieving successful aerosol delivery to patients. Some recent advances include the use of "smart inhalers." These smart inhalers were developed to improve patients' adherence by helping them administer their medications appropriately and on time. In recent years, the focus has been on achieving drug delivery consistency across a range of flow rates while providing simple operation steps and the capability to deliver greater payloads of drugs to the airways. Nebulizers have been engineered to be more portable and uniform, and they are becoming more efficient by generating smaller aerosols and cooperating with patients' breathing. Also, new propellant systems attempt to improve the aerosol performance delivered by pMDIs.

Smart Inhalers

SmartMist® and AERx®, developed by Aradigm Corporation in the 1990s, were early generation smart inhalers that could monitor compliance and assist patients to inhale drugs properly supported by a microprocessor (69,100,101). The inspiratory data were saved in solid-state memory for later retrieval *via* a personal computer (100).

Smart inhalers recently use electronic monitoring systems that connect to the Internet or to other devices. They have been developed to improve patient's adherence to inhaled medications, and they reduce errors induced by devices or patients. They have been introduced to the market for only a short time, but several analysts have predicted steep growth of this technology (102–104) due to the potential benefits of enhanced adherence to their medications and the ability to track patient compliance and use. Smart inhalers not only remind patients to

take a dose; they also record and transfer usage data, which may improve adherence (20–22,105,106). Advanced features available from newly developed smart inhalers may help minimize patient errors. These features include step-by-step guidance provided from the inhaler's screen (107) and inhalation profile monitoring (107,108).

Smart inhalers generally fall into two categories: *add-on* and *originally integrated* devices. Examples of add-on devices include those available from Propeller Health, Adherium Ltd., and Teva Pharmaceutical Industries Ltd. Originally integrated devices include examples developed by 3M™ Drug Delivery Systems, Novartis Pharmaceuticals, and Teva Pharmaceuticals.

Since 2010, Propeller Health has developed inhaler device sensors, mobile applications, analytics, and regular feedback to record the usage of respiratory medications (109). The Propeller platform maintains a database of when and where patients use their inhalers (109,110). Since the first FDA clearance in 2012 (111), this system has been adapted to several inhaler device types, including devices such as Novartis' Breezhaler®, Boehringer Ingelheim's Respimat®, GlaxoSmithKline's Diskus® and Ellipta®, and other MDIs (109,112). It has been reported that the use of the platform from Propeller Health improved asthma control: There was a 78% decrease in rescue inhaler use and a 48% increase in symptom-free days for residents in Jefferson county in Kentucky (113). However, these results excluded participants who did not sync their usage data more than 60 days, and the average time that participants remained synced was 273 days, while the results extended over 365 days.

Adherium Ltd., which was renamed from Nexus6 Ltd. in June 2015, also markets the Hailie™, previously known as the Smartinhaler™ platform before May 2018 (114). The Hailie™ tracks the date and time of medication usage, reminds users to dose, and sends usage data to a mobile application *via* Bluetooth technology (115). This inhaler monitoring device received 510(k) marketing clearance from the FDA in June 2014 (116). Chan *et al*. conducted a clinical study of 220 children, ages 6–15, in New Zealand. Their study indicated that using SmartTrack, a previous version of the Hailie™, improved adherence to medication by 180% and reduced the use of reliever medication by 45% (20). A clinical study with SmartTrack also showed a 59% improvement of adherence to medication with adults (22).

Teva Pharmaceutical Industries Ltd. joined the group of firms developing smart inhalers after it acquired Gecko Health Innovations (117), which was founded in 2012 in Massachusetts. Like other add-on smart inhalers, CareTRx™ is a Cloud-based solution that contains a universally designed hardware that can be attached to standard MDI canisters. This attachment transforms a typical inhaler into a smart inhaler for enhancing a patient's adherence to medications (118). With CareTRx™, patients can set reminders for medications; track all types of medications; record symptoms, triggers, and peak flow; view charts and statistics on activity; and review trends for adherence. It also connects patients to care providers to enhance communication (119,120).

Intelligent Control Inhaler, an originally integrated device developed by 3M™ Drug Delivery System, was introduced in April 2016 (121). The Intelligent Control Inhaler is designed as a breath-actuated pMDI with simple open–inhale–close operation steps (122). This pMDI reduces errors caused by a patient's breath profile through the use of step-by-step on-screen guides and through the control of inspiratory flow rate during inspiration (122,123). In addition, to increase dose accuracy, the dose as well as inspiration profiles is recorded only when correctly inhaled by the patient (124).

Novartis is also developing its own new smart device for dry powder inhalation, USSC-03 (108). The USSC-03 device contains two functional parts: a cartridge and an inhaler body (108). Two different versions of the body are available: a mechanical body and an electronic body. The cartridge can fit in either one (108). Unlike the mechanical version that operates without electronics, the electronic version has a series of illuminated indicators and can monitor the usage time, date, and inhalation profile, all of which can be transferred wirelessly to a hub *via* Bluetooth (108). In the electronic device, the breath-actuated blister access mechanism embedded in the device does not pierce the blister until a pressure drop reaches around 1.5 kPa due to the patient's inhalation. This feature, along with the simple open_inhale–close operation steps, can reduce errors associated with low inspiratory flow rate or misuse by the patient (108,125).

The drug formulation used for USSC-03 is comprised of small porous particles made by PulmoSphere® (125). Due to its advantages in particle engineering and device technologies, the total lung deposition by USSC-03 is independent of the patient's inspiratory flow rate when it is above 1.0 kPa (125). The drug powder is emitted from the device within the first 0.2 L of inhaled volume; thus, it is well suited for patients with decreased inspiratory volume (125).

Another new smart device for dry powder inhalation was recently introduced by Novartis. The Electronic Breezhaler® was developed from the marketed Breezhaler®, integrating electronics that can sense, record, and communicate usage data (126). While the appearance of the electronic Breezhaler® is very similar to existing Breezhaler®, it is slightly larger. The study by Colthorpe *et al*. demonstrated that the electronic Breezhaler® has usability and performance that is equivalent to the existing Breezhaler® (126).

In addition to CareTRx™, Teva Pharmaceuticals Industries has tested an electronic, module-integrated *multidose dry powder inhaler* (MDPI) (127). The integrated electronic module records usage time, peak inspiratory flow rate, and acceleration rate, as well as inhaled volume.

These devices, however, represent a new technology that faces possible limitations of high cost, patient avoidance of sharing personal information and data, and low market share in developing countries. First, smart inhalers could initially be more expensive than conventional devices (128), and their extra cost may not be fully covered by the patient's insurance until more economic benefit is demonstrated (129). Other obstacles to this technology that will need to be overcome include data security, developing world access, and product robustness as well as patient reluctance due to privacy concerns.

Even with these possible limitations, smart inhalers still provide features that are of value to the patient and the healthcare system as a whole. Smart inhalers received positive feedback from patients in reported studies (130), and they improved patient's adherence as well as their clinical outcomes (20,105,131). The improved adherence could reduce the excessive waste of prescription drugs (132) that reduces total cost of the treatment and contamination of drinking water by drug waste (133). In addition, smart inhalers also provide benefits during clinical trials by providing adherence

data. The drugs delivered by smart inhalers can be determined more precisely if it is effective with patients who actually adhere to the medication (134).

DPIs

DPIs can be divided into two groups according to their mechanisms of powder aerosolization: *active* DPIs and *passive* DPIs (10). The active DPI consists of an integrated energy source to aerosolize the powder inside the device. Therefore, aerosolization is not dependent on the patient's inspiratory flow rate (10). The aerosolization of the powder of passive DPI, however, is dependent on the patient's inspiratory flow rate (10). Active DPIs have been developed, such as the Taper by 3M™ and Spiros® by Dura Pharmaceuticals; however, all DPIs currently on the market are passive DPIs.

DPIs are typically breath-actuated devices triggered by the patient's inhalation with appropriate timing. Thus, DPIs do not require hand–breath coordination to minimize patient errors, while hand–breath coordination is required by conventional pMDIs during drug administration (135). Therefore, DPIs can successfully minimize patient coordination of actuation due to breath-actuated functions, but the efficiency and consistency of drug delivery and aerosol dispersion by DPIs may still be dependent on the patient's inspiratory flow rate, which has been an important challenge for pulmonary drug delivery using DPIs (127,136,137).

As an illustration in Fig. 3, an inhaler tested at different inspiratory flow rates demonstrated that the output of total lung deposition could be decreased up to 50% when the inspiratory flow rate dropped from 60 to 30 L/min (137,138). Olsson *et al.* reported that *in vivo* total lung deposition of the Albuterol® Turbuhaler®, when measured using the charcoal-block method, dropped to a 13.9% nominal dose at a weak peak inspiratory flow rate (*i.e.*, mean attained peak flows of 34 L/min), while the nominal dose was 23.2% at a moderate peak inspiratory flow rate (mean attained peak flows of 62 L/min) (139). Ung *et al.* also demonstrated that the *in vitro* lung dose fraction of the Asmanex® Twisthaler® decreased from a 32% nominal dose at a peak inspiratory flow rate of 57 L/min to a 15% nominal dose at a peak inspiratory flow rate of 33 L/min (140). Newly described devices, however, seem to successfully overcome this inconsistency of drug delivery caused by low flow rates, and they also have achieved better aerosol performance.

Grant *et al.* reported on the dose consistency of Ellipta®, a next-generation DPI developed by GlaxoSmithKline, and the *in vitro* results demonstrated consistent and reliable dose delivery at tested flow rates of 30–90 L/min (141). The delivered dose range of fluticasone furoate was 87.6–96.9% of the nominal blister contents, and the fine particle dose range was 20.7–25.4% for delivered fluticasone furoate from Breo® Ellipta® 100/25 over the flow rate range of 30–90 L/min (141). Ellipta® is designed as a breath-actuated DPI with simple open–inhale–close operation steps to minimize errors. Recent studies demonstrate that patients preferred Ellipta® to previously marketed DPIs such as Handihaler® (142,143), Diskus® (143,144), Turbuhaler® (143), and Breezhaler® (143) due to these simple steps to take medications. However, patient preference studies frequently report positive outcomes for the tested device over others, and these results should be interpreted with caution (145).

RespiClick® is another newly developed breath-actuated DPI with simple operation steps. The study of the inhalation parameters of RespiClick®, evaluated in children, adolescents, and adults, shows that RespiClick® also requires a peak inspiratory flow rate of only 30 L/min (146). This rate is applicable regardless of age and disease severity after appropriate training (147). In the case of the Proair® RespiClick®, the device delivering albuterol sulfate can treat or prevent bronchospasm in patients over 4 years old who have reversible obstructive airway disease (146,148).

A disposable, capsule-free device that consists of only two components also generates high respirable aerosols at a relatively low flow rate. The TwinCaps®, developed by Hovione, keeps powder for two dosages in its shuttle, which is leak proof (149) and can achieve over 70% FPF at 35 L/min

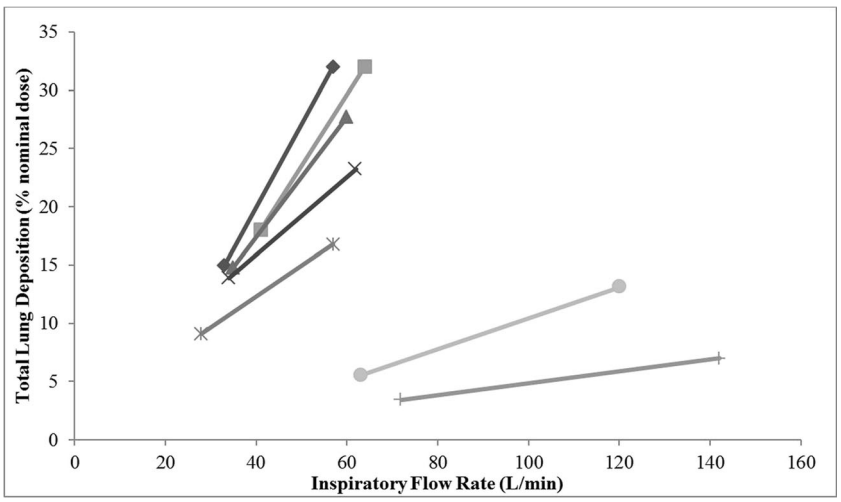

Fig. 3. Impact of flow rate on the deposition of pharmaceutical aerosols. Diamond, Asmanex Twisthaler; square, Budesonide Flexhaler; triangle, Pulmicort Turbuhaler; times symbol, Albuterol Turbuhaler; asterisk, Bricanyl Turbuhaler; circle, Neodocromil Spinhaler; plus sign, Ventolin Rotahaler (137). Data reproduced with permission from Springer Nature

(at 4 kPa) when tested with amorphous spherical composite particles of 80% trehalose and 20% leucine (149,150).

The Twister®, developed by Aptar Pharma, also provides consistent dose and FPF at a flow rate of 40–80 L/min when tested *in vitro* (151), with a unique feature of opening the capsule during inhalation rather than piercing before inspiration (152). With a low number of components and a transparent, simple design, the Twister is cost effective and can minimize the drawbacks associated with pierced-capsule platforms, which include piercing inconsistency, powder remaining in the capsule, and inhaling capsule debris made by piercing.

Like other newly developed DPIs, NEXThaler® also requires an inspiratory flow rate of only 30 L/min to trigger the products (153). Buttini *et al.* demonstrated the *in vitro* aerodynamic performance of NEXThaler® (154). Their results showed that the Foster® NEXThaler®, a fixed dose of beclomethasone dipropionate and formoterol fumarate, exhibited a consistent delivered dose of 81.1–88.2% at a range of flow rates of 30–90 L/min (see Fig. 4). Also, the decrease in fine particle mass was 17% for beclomethasone dipropionate and 24% for formoterol fumarate when the flow rate dropped from 90 to 30 L/min (154).

In addition to dose consistency at a range of inspiratory flow rates from newly developed DPIs, some new DPIs are capable of high-dose delivery (see Table II). The TOBI® Podhaler® exhibits flow rate independence when delivering doses to the lung as shown in Fig. 5 (160), and it is designed to deliver 112 mg with only four inhalations (155). The Twincer™ (158) is also capable of delivering a large dose, and the maximum dose loading of the Orbital® (157) is 400 mg with multiple applications. Young *et al.* compared the aerosol performance of the Orbital® and the Plastiape RS01. The FPF of the Orbital® was up to 67% higher than that of RS01 (157). In addition, the TwinMax®, structured almost the same as the TwinCaps®, has an enlarged powder cavity for delivering larger drug doses. It was developed from the TwinCaps® platform using 3D printing technology (159). When tested with 100 mg of synthetic protein, TwinMax® had an FPF of 39% with an emitted dose of 80% (159), showing the opportunity to deliver biologics and other drugs requiring high dosage.

While new DPI designs have led to improved performance, existing DPIs have shown marked improvement in performance through the addition of add-on aerosol-enhancing devices. Respira Therapeutics, Inc. has developed a small dispersion engine, named, the *axially oscillating sphere* (AOS), which can be simply attached to the mouthpiece or capsule chamber of a device (139,161). With the tested formulations, Hannon *et al.* demonstrated that the AOS dispersion engine successfully achieved the enhancement of fine particle doses less than 3 μm (1.5–2.6×) at 4 kPa pressure drop when attached to the Diskus®, Handihaler®, or Plastiape RS01 at a dose range of 12–4000 μg (139). The data support that the dispersion engine can improve the aerosol performance of off-the-shelf devices while simply being attached to them (139).

Nebulizers

Breath-enhanced, breath-actuated, and vibrating mesh nebulizers have been developed to improve delivery efficiency and to produce smaller aerosols (10). Breath-enhanced jet nebulizers, such as the Pari LC® Plus, and the Side Stream Plus®, have been developed to increase the output rate and decrease the administration time (162) by a turbocharged effect when patients are inhaling, and using two 2-way valves to minimize the loss of aerosol when patients are exhaled (163). Breath-actuated nebulizers, such as the AeroEclipse®, are designed to deliver aerosol only during inspiration. Therefore, the loss of drug is reduced, since no aerosol is generated during exhalation (164).

Vibrating mesh nebulizers, such as the Pari eFlow® rapid, the Micro Air® NE-U22, and the Aeroneb® Go include a fine mesh plate to generate aerosol. The size of the aerosol produced by vibrating mesh nebulizers is affected by the diameter of the mesh or by the aperture size (165). They can generate very fine aerosols (166) that can be deposited in the alveoli with high efficiency (1). Skaria and Smaldone (167) tested radiolabeled albuterol (2.5 mg per 3 mL) and

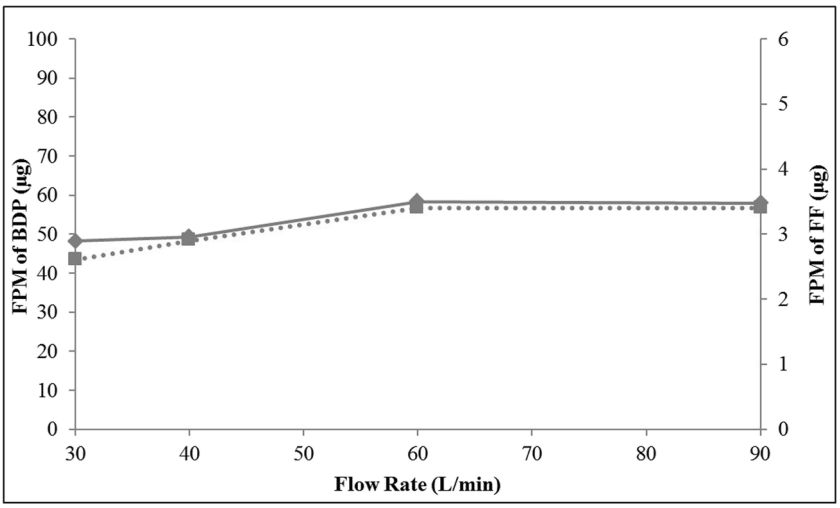

Fig. 4. Flow rate independence in a fine particle mass (FPM) of (diamond) beclomethasone dipropionate (BDP) and (square) formoterol fumarate (FF) by the Foster® NEXThaler® (154)

Table II. DPIs Delivering Large Doses

Device	Dose loading (mg)	Aerosol performance	Reference
Podhaler®	28	PulmoSphere® tobramycin: FPF 69%	(155,156)
Orbital®	Up to 400	Spray-dried ciprofloxacin: FPF 67% PulmoSphere® tobramycin: FPF 61%	(157)
Twincer®	10–50	Colistimethate sodium: FPF 63.5%	(158)
TwinMax™	100	Synthetic protein: FPF 39%	(159)

FPF fine particle fraction

found that the inhaled mass of the NE-U22 was twice as much as the Sidestream® jet nebulizer (20 *vs.* 10% of nebulizer charge, respectively), while the MMAD for both was similar. Also, the residual drug remaining in the NE-U22 was significantly less than in the Sidestream® (Fig. 6).

The aperture diameter directly correlates with the aerosol size and output rate (165,169). Therefore, a slower output rate can be achieved using a smaller aerosol size. The *photo-defined aperture plate* (PDAP) is a new technology for nebulization (169). PDAP, with a novel 2-layer architecture, allows for the decoupling of output flow rate from aerosol size, and it is expected to employ a faster aerosol output rate (169). In PDAP, up to 20 small apertures are positioned in a thicker inlet with a larger diameter aperture (170).

Fink *et al.* compared the particle size distribution and output rate of a viscous formulation generated by a conventional vibration mesh nebulizer and PDAP (170). Their results show that PDAP has a smaller volume and mean diameter than conventional vibrating mesh (1.05 *vs.* 3.5 μm, respectively), and it also has a faster output rate (0.33 *vs.* 0.05 mL/min, respectively). These results support the possibility of more efficient delivery and the development of inhaled medications especially for critically ill patients, from neonates to adults, who require ventilator support (170).

Vibrating mesh nebulizers have many advantages over other types of nebulizers, such as small size, high portability, silent operation, and increased output efficiency (163,166).

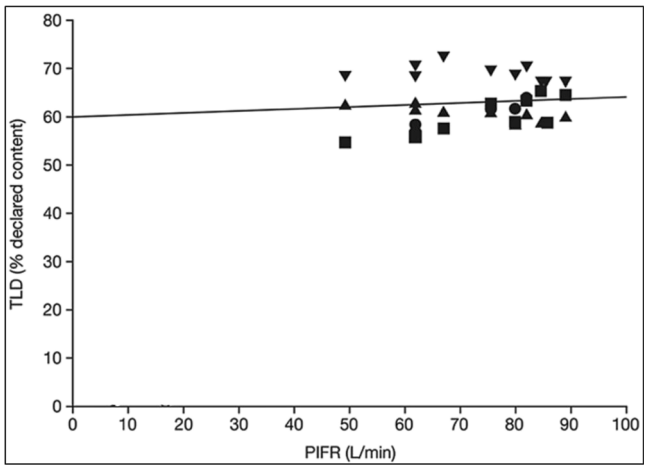

Fig. 5. Peak inspiratory flow rate (PIFR) independence in total lung dose (TLD) observed for the TOBI® Podhaler® (160). The lines represent linear regressions. The various symbols represent the mean values for various Alberta-idealized throats (circle, child; square, small adult; inverted triangle, large adult). Modified figure reproduced with permission from John Wiley and Sons

However, the pores on the mesh have been reported to clog easily, and it can be difficult to observe the blockage and remove it (171). To reduce clogging due to multiple use, the MicroBase μSMI was developed by Hsiao *et al.* (168). The disposable medication container and mesh are separated from the vibrating module of the MicroBase μSMI and nebulization occurs only when they are in contact as shown in Fig. 7 (168). When a budesonide suspension was tested (1 mg per 2 mL), the MicroBase μSMI performed with a significantly higher respirable dose (23%), than the Aerogen Solo, Philips InnoSpire Go, or Pari eRapid (15, 11, and 5%, respectively) (168).

Conventional jet nebulizers have also been improved in recent years. Improvement in efficiency has been enabled by adding a horizontal venturi inside the nebulizer (173). While the basic principle of a *horizontal venturi nebulizer* (HVN) is similar to typical nebulizers, the horizontal venturi installed inside is intended to reduce the required air flow rate to deliver aerosol, which can be nebulized as ultra-fine particles (174). Primary droplet formation is fine-tuned by the flow rate of the compressed gas and by the horizontal and vertical orifice diameters that control the feed rate of formulations (174). A baffle downstream from the nozzle can control the final particle size distribution (174). The particle size distribution depends on the size of the horizontal nozzle and the distance between the baffle and the horizontal nozzle (174). The baffle allows only small particles to pass through the airstream; large particles are recycled back to the reservoir (174).

When tested to deliver an albuterol sulfate solution, HVN delivered a much larger amount (190.9 μg) of the formulation compared to the Pari® LC Plus nebulizer (21.1 μg) using only half flow rate (3 and 6 L/min, respectively) (174). Particle size distribution by the Anderson cascade impactor showed that 54.9% of the delivered dose of the albuterol sulfate solution was measured as ultra-fine particles smaller than 0.4 μm (174). With a higher delivered dose at a lower gas flow rate, HVN provides less ambient drug loss during expiration, as well as more efficient delivery to the lower respiratory tract (174).

A new mechanism of nebulization has also been suggested. *Surface acoustic waves* (SAWs) travel only along the surface of a material due to their relatively short wavelengths, which cannot penetrate a material deeply. Many applications related to SAWs are involved in electronics such as semiconductors (175) and laser detectors (176); however, one application of SAWs using high frequencies (10 to 100 MHz) has been evaluated for the purpose of nebulization (177).

When SAWs travel, they accelerate as much as 10 million times the acceleration of gravity on the surface of the fluid, conducting nebulization from the surface above a critical

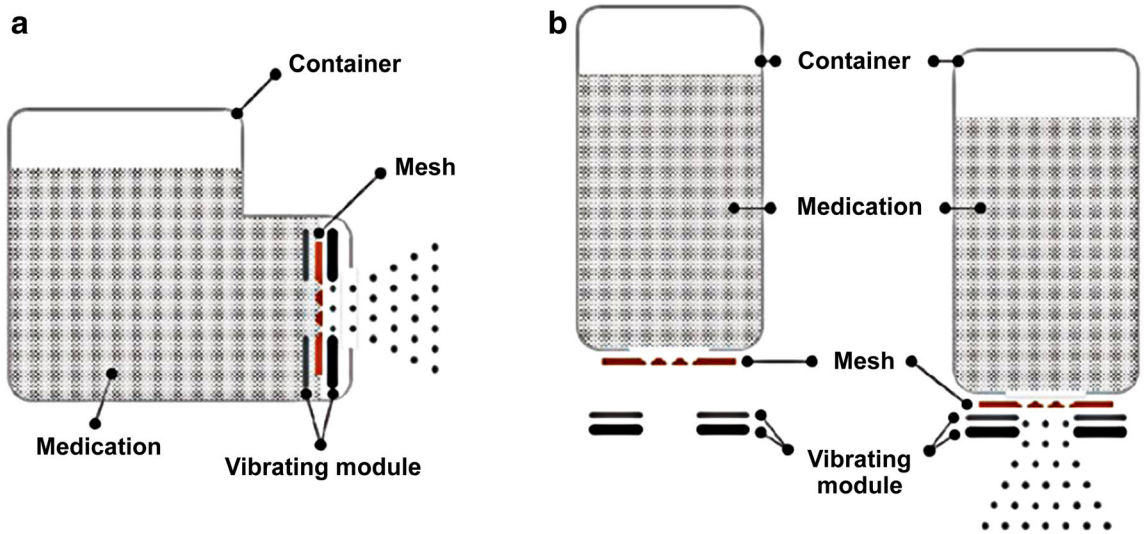

Fig. 6. **a** Illustration of traditional vibrating mesh. **b** Contact-triggered vibrating mesh medication cup (168). Reproduced with permission from Respiratory Drug Delivery 2018, Virginia Commonwealth University and RDD Online

velocity displacement amplitude (178), which is caused by the destabilization and breakup of its interface (179). The droplets produced by SAW-induced nebulization can be tuned to a size range of 1–5 μm with a nebulization rate of 0.1–0.6 mL/min (177), which is ideal for pulmonary delivery (180). These high frequencies require very low input power (1 W) for nebulization; hence, they provide macromolecules less chance to be damaged during aerosolization, compared with the ultrasonic nebulization, which typically requires 20 kHz to 3 MHz (179,181).

While a study of nebulizing proteins by SAWs is not reported yet, Wang *et al.* reported on the stability and efficacy of a synthetic model of antimicrobial peptides nebulized by SAWs (181). In their *in vitro* study, about 70% of nebulized peptides were within the optimal size range for pulmonary delivery, as characterized by the *next-generation impactor* (NGI). Mass spectrometry confirmed that they were retained. The peptide recovery concentration after nebulization was found to be significantly higher than 90%, indicating that the peptide loss from nebulization was insignificant. These results show that SAW-induced nebulization is a potential technique for the delivery of both small molecules and macromolecules through pulmonary pathways with minimal energy input to the drug.

Soft Mist Inhalers

The first soft mist inhaler developed by Boehringer Ingelheim was introduced to the market in 2011. The Respimat® Soft Mist™ inhaler remains the only soft mist inhaler approved by the FDA (182). Recently, Dance Biopharm Inc. introduced another soft mist inhaler to the market: the Dance-501. The Dance-501 is a combination product that consists of a small, handheld electronic inhaler and an aqueous liquid insulin formulation stored in a sterile dispenser (183). The Respimat® is operated with mechanical energy from a spring to generate aerosols from a drug solution in the cartridge (184) that is then passed through a uniblock to generate an aerosol.

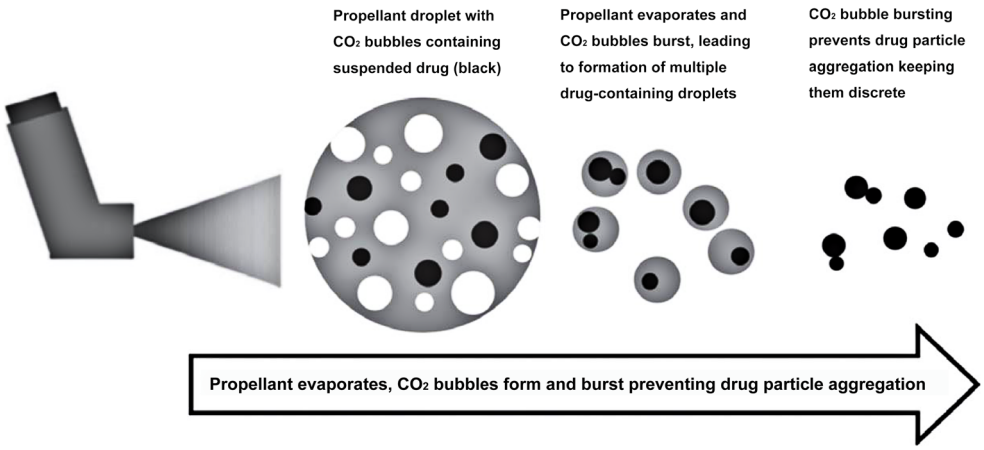

Fig. 7. Schematic diagram showing how the effervescence caused by CO_2 in an HFA-134a/EtOH system might prevent primary drug particles from forming a large aggregate as a single droplet evaporates (172). Reproduced with permission from Respiratory Drug Delivery, Virginia Commonwealth University and RDD Online

However, the Dance-501 is operated using small battery and aerosolizes a drug solution by a vibrating mesh technology that was incorporated into the device (185). The tasteless insulin formulation is stable at room temperature for multiple weeks after opening (186). Only a few breaths are required to complete a dosage without the coughing that is generally observed in patients using DPIs (183). The Dance-501 has currently completed phase II clinical trials (186).

pMDIs

Among orally inhaled products, pMDIs have been the most common device used to deliver medicines to the lung to treat local pulmonary diseases since their development in 1955 (10,163). This prevalence is due to their compact, portable, easy to use, and convenient multidose design combined in a single device (163).

Even with many advantages on pMDIs, requiring proper patients' hand-inspiration, coordination is a significant challenge for using pMDIs. To improve this, Clement Clarke International introduced the Flo-Tone® training device that can be attached to the mouthpiece of a pMDI and provide an audible signal with the patients' corresponding inspiratory flow rate of 30–60 L/min (187). Significantly fewer inhaler technique errors were observed when patients were trained using verbal counseling and Flo-Tone® compared with patients with only verbal counseling (187).

Due to the *Montreal Protocol*, however, pMDIs using chlorofluorocarbons (CFCs) as a propellant were recalled from the market. Hydrofluoroalkane (HFA) quickly became the next-generation propellant for pMDIs. The FDA approved eight pMDIs using HFA in a relatively short time between 2004 and 2006. However, pMDIs using high-pressure HFA are not suitable for the delivery of many drugs (188), including biologics, due to their typically small dose range per actuation (189) and their physicochemical instability. In addition, common propellants, HFA-134a and HFA-227, are not ideal for drugs that have poor solubility, due to nozzle blockage, agglomeration, sedimentation, and nonhomogeneity of suspension (190). Ethanol is often used to improve solubility. Gupta *et al.* evaluated the relationship between ethanol concentration and a maximum respirable mass to optimize delivering beclomethasone dipropionate by pMDI (191). However, many problems still exist: A large amount of ethanol induces large droplet sizes and is not acceptable for younger patients (190). To address these problems, a new propellant system is required.

Recently, 1,1-difluoroethane (HFA-152a) has been considered as a new propellant for MDI (192,193). Corr and Noakes have compared the solubility of salbutamol sulfate in HFA-134a and HFA-152a, and they found that the solubility in HFA-152a was much higher (2.5% *w*/*w* compared to 0.05% *w*/*w*) (192). The solubility of lecithin, PEG 400, oleic acid, and SPAN®80 in HFA-152a was also higher than their solubility in HFA-134a (192,194). Moreover, using salbutamol sulfate in an HFA-152a MDI formulation without ethanol exhibits significantly higher FPF (192) and a longer time to sediment (194). Therefore, HFA-152a could be a solution to address the problems caused by ethanol and other current propellant systems.

Keller *et al.* also introduce a new propellant system for pMDIs (195). The addition of carbon dioxide (CO_2) was suggested to improve not only the wetting properties of drug substances but also particle size distribution (195). By using this new propellant system, Kelkar and Dalby have shown that CO_2 added to HFA-134a and ethanol as a propellant system can improve the aerodynamic particle size distribution (172,196). When compared to a formulation containing HFA-insoluble helium, a beclomethasone dipropionate (BDP) formulation containing CO_2 exhibited a smaller particle size distribution in all of the tested concentrations (BDP 0.025–0.080% *w*/*w*) (196). Two proposed mechanisms for the CO_2 contribution to smaller particle size are propellant evaporation from the particle surface and the rapid expansion of CO_2 (196) (see Fig. 8). In addition to the advantage of smaller particle size, this new propellant system also exhibits a decreased plume angle and width (23.7° and 29.5 mm) compared to HFA-134a (30.8° and 38.7 mm), which could lead to lower throat deposition (197).

CONCLUSION

Orally inhaled products have greatly improved through the application of new technological advances in both formulation

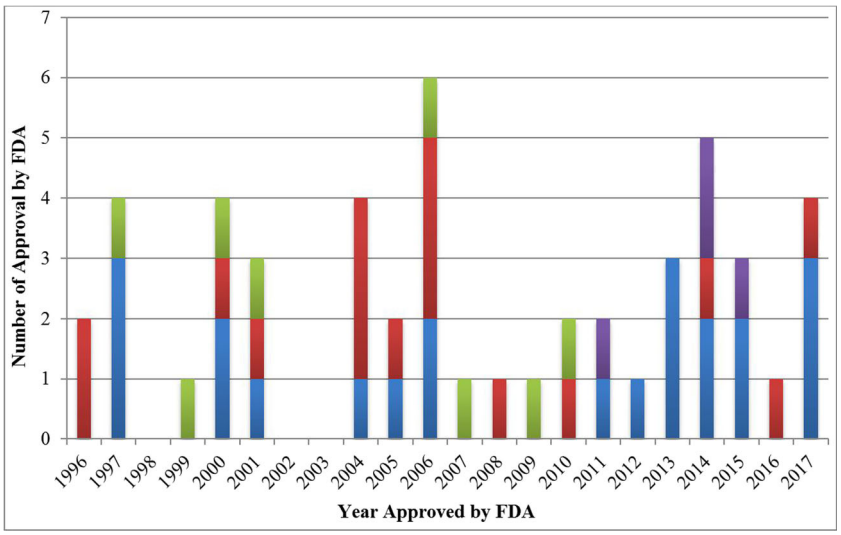

Fig. 8. Number of FDA-approved OIPs between 1996 and 2017 by year. Blue: DPI. Red: pMDI. Green: nebulizer. Purple: Soft Mist inhaler (12)

and devices. Formulation advances have been focused on enhancing aerosol performance by controlling particle density, size, shape, and surface energy. Newly developed smart inhalers help patients use these devices appropriately, stick to regimens, and track their adherence. Design improvements in other types of devices provide easier and more straightforward operation processes while enhancing delivery efficiency and dose consistency. Through improvement in formulation, device, and monitoring technologies, orally inhaled products can continue to improve patient outcomes and reduce the burden of lung disease on the healthcare system.

REFERENCES

1. Laube BL, Janssens HM, de Jongh FHC, Devadason SG, Dhand R, Diot P, et al. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J. 2011;37(6):1308–31.
2. Depreter F, Pilcer G, Amighi K. Inhaled proteins: challenges and perspectives. Int J Pharm. 2013;447(1–2):251–80.
3. Hansel TT, Barnes PJ. New drugs for asthma, allergy, and COPD. Basel: Karger; 2001. x, 389 p.
4. Hoppentocht M, Hagedoorn P, Frijlink HW, de Boer AH. Developments and strategies for inhaled antibiotic drugs in tuberculosis therapy: a critical evaluation. Eur J Pharm Biopharm. 2014;86(1):23–30.
5. Newman SP, Pavia D, Moren F, Sheahan NF, Clarke SW. Deposition of pressurised aerosols in the human respiratory tract. Thorax. 1981;36(1):52–5.
6. Lewis RA, Fleming JS. Fractional deposition from a jet nebulizer: how it differs from a metered dose inhaler. Br J Dis Chest. 1985;79(4):361–7.
7. Newman SP, Hollingworth A, Clark AR. Effect of different modes of inhalation on drug delivery from a dry powder inhaler. Int J Pharm. 1994;102(1–3):127–32.
8. Lindert S, Below A, Breitkreutz J. Performance of dry powder inhalers with single dosed capsules in preschool children and adults using improved upper airway models. Pharmaceutics. 2014;6(1):36–51.
9. Wang Y-B, Watts AB, Peters JI, Williams RO 3rd. The impact of pulmonary diseases on the fate of inhaled medicines—a review. Int J Pharm. 2014;461(1–2):112–28.
10. Ibrahim M, Verma R, Garcia-Contreras L. Inhalation drug delivery devices: technology update. Med Devices (Auckl). 2015;8:131–9.
11. Stein SW, Sheth P, Hodson PD, Myrdal PB. Advances in metered dose inhaler technology: hardware development. AAPS PharmSciTech. 2014;15(2):326–38.
12. Drugs@FDA: FDA approved drug products [Internet]. U.S. Department of Health and Human Services. [cited July 2, 2018]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/.
13. Pfutzner A, Forst T. Pulmonary insulin delivery by means of the Technosphere drug carrier mechanism. Expert Opin Drug Deliv. 2005;2(6):1097–106.
14. Griffin DE. Current progress in pulmonary delivery of measles vaccine. Expert Rev Vaccines. 2014;13(6):751–9.
15. Luinstra M, Grasmeijer F, Hagedoorn P, Moes JR, Frijlink HW, de Boer AH. A levodopa dry powder inhaler for the treatment of Parkinson's disease patients in off periods. Eur J Pharm Biopharm. 2015;97(Pt A):22–9.
16. LeWitt PA, Pahwa R, Sedkov A, Corbin A, Batycky R, Murck H. Pulmonary safety and tolerability of inhaled levodopa (CVT-301) administered to patients with Parkinson's disease. J Aerosol Med Pulm Drug Deliv. 2018;31(3):155–61.
17. Fathe K, Ferrati S, Moraga-Espinoza D, Yazdi A, Smyth HD. Inhaled biologics: from preclinical to product approval. Curr Pharm Des. 2016;22(17):2501–21.
18. Silveira FP, Abdel-Massih R, Bogdanovich T, Pakstis DL, Routh RL, Moss RB. Treatment of resistant influenza virus infection in a hospitalized patient with cystic fibrosis with DAS181, a host-directed antiviral. Antivir Ther. 2016;21(1):71–4.
19. Morales JO, Fathe KR, Brunaugh A, Ferrati S, Li S, Montenegro-Nicolini M, et al. Challenges and future prospects for the delivery of biologics: oral mucosal, pulmonary, and transdermal routes. AAPS J. 2017;19(3):652–68.
20. Chan AH, Stewart AW, Harrison J, Camargo CA Jr, Black PN, Mitchell EA. 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. 2015;3(3):210–9.
21. Charles T, Quinn D, Weatherall M, Aldington S, Beasley R, Holt S. An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma. J Allergy Clin Immunol. 2007;119(4):811–6.
22. Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. J Allergy Clin Immunol. 2014;134(6):1260–8 **e3**.
23. Smyth HDC, Hickey AJ. In: Rathbone M, editor. Controlled pulmonary drug delivery. 1st ed. New York: Springer; 2011.
24. Dunbar CA, Hickey AJ, Holzner P. Dispersion and characterization of pharmaceutical dry powder aerosols. Kona Powder Part J. 1998;16:7–45.
25. Byron PR. Prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation. J Pharm Sci. 1986;75(5):433–8.
26. Newman SP, Chan HK. In vitro/in vivo comparisons in pulmonary drug delivery. J Aerosol Med Pulm Drug Deliv. 2008;21(1):77–84.
27. Hassan MS, Lau RW. Effect of particle shape on dry particle inhalation: study of flowability, aerosolization, and deposition properties. AAPS PharmSciTech. 2009;10(4):1252–62.
28. Ikegami K, Kawashima Y, Takeuchi H, Yamamoto H, Isshiki N, Momose D, et al. Improved inhalation behavior of steroid KSR-592 in vitro with Jethaler by polymorphic transformation to needle-like crystals (beta-form). Pharm Res. 2002;19(10):1439–45.
29. Larhrib H, Martin GP, Marriott C, Prime D. The influence of carrier and drug morphology on drug delivery from dry powder formulations. Int J Pharm. 2003;257(1–2):283–96.
30. Chan H-K. What is the role of particle morphology in pharmaceutical powder aerosols? Expert Opin Drug Deliv. 2008;5(8):909–14.
31. Dellamary LA, Riess J, Schutt EG, Weers JG, Tarara TE, inventors. Novartis, assignee. Stable metal ion-lipid powdered pharmaceutical compositions for drug delivery and methods of use. patent US7871598 B1. 2011.
32. Weers J, Tarara T. The PulmoSphere platform for pulmonary drug delivery. Ther Deliv. 2014;5(3):277–95.
33. Vehring R. Pharmaceutical particle engineering via spray drying. Pharm Res. 2008;25(5):999–1022.
34. Wilson BR, Grant ML, Steiner SS, Pohl R. TECHNOSPHERES™ for pulmonary and nasal applications. Respir Drug Deliv. 2002;2:545–8.
35. Beinborn NA, Du J, Wiederhold NP, Smyth HD, Williams RO 3rd. Dry powder insufflation of crystalline and amorphous voriconazole formulations produced by thin film freezing to mice. Eur J Pharm Biopharm. 2012;81(3):600–8.
36. Tarara TE, Weers JG, Dellamary L. Engineered powders for inhalation. Respir Drug Deliv. 2000;2:413–6.
37. Newhouse MT, Hirst PH, Duddu SP, Walter YH, Tarara TE, Clark AR, et al. Inhalation of a dry powder tobramycin PulmoSphere formulation in healthy volunteers. Chest. 2003;124(1):360–6.
38. Bot AI, Tarara TE, Smith DJ, Bot SR, Woods CM, Weers JG. Novel lipid-based hollow-porous microparticles as a platform

for immunoglobulin delivery to the respiratory tract. Pharm Res. 2000;17(3):275–83.
39. Dellamary LA, Tarara TE, Smith DJ, Woelk CH, Adractas A, Costello ML, et al. Hollow porous particles in metered dose inhalers. Pharm Res. 2000;17(2):168–74.
40. Haynes A, Nakamura J, Heng C, Heuerding S, Thompson G, Malcolmson RJ. Aerosol performance of tobramycin inhalation powder. Respir Drug Deliv. 2010;3:701–6.
41. Weers JG, Ung K, Chan L, Glusker M, Ament B, Le J, et al. Minimizing human factor effects through improved inhaler design. Respir Drug Deliv. 2012;1:217–26.
42. Miller DP, Tan T, Nakamura J, Malcolmson RJ, Tarara TE, Weers JG. Physical characterization of tobramycin inhalation powder: II. State diagram of an amorphous engineered particle formulation. Mol Pharm. 2017;14(6):1950–60.
43. Tarara TE, Hartman MS, Gill H, Kennedy AA, Weers JG. Characterization of suspension-based metered dose inhaler formulations composed of spray-dried budesonide microcrystals dispersed in HFA-134a. Pharm Res. 2004;21(9):1607–14.
44. Kirkpatrick WR, Najvar LK, Vallor AC, Wiederhold NP, Bocanegra R, Pfeiffer J, et al. Prophylactic efficacy of single dose pulmonary administration of amphotericin B inhalation powder in a guinea pig model of invasive pulmonary aspergillosis. J Antimicrob Chemother. 2012;67(4):970–6.
45. Weers JG, Tarara TE, Malcolmson RJ, Leung D. Embedded crystals in low density particles: formulation, manufacture, and properties. Respir Drug Deliv. 2006;1:297–306.
46. McShane PJ, Weers JG, Tarara TE, Haynes A, Durbha P, Miller DP, et al. Ciprofloxacin dry powder for inhalation (ciprofloxacin DPI): technical design and features of an efficient drug-device combination. Pulm Pharmacol Ther. 2018;50:72–9.
47. De Soyza A, Aksamit T, Bandel T-J, Criollo M, Elborn JS, Operschall E, et al. RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J. 2018;51(1):1702052.
48. Aksamit T, De Soyza A, Bandel T-J, Criollo M, Elborn JS, Operschall E, et al. RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J. 2018;51(1):1702053.
49. Lechuga-Ballesteros D, Noga B, Vehring R, Cummings RH, Dwivedi SK. Novel cosuspension metered-dose inhalers for the combination therapy of chronic obstructive pulmonary disease and asthma. Future Med Chem. 2011;3(13):1703–18.
50. Vehring R, Lechuga-Ballesteros D, Joshi V, Noga B, Dwivedi SK. Cosuspensions of microcrystals and engineered microparticles for uniform and efficient delivery of respiratory therapeutics from pressurized metered dose inhalers. Langmuir. 2012;28(42):15015–23.
51. Hartman M, Tarara TE, Teung P, Weers JG, inventors. Novartis, assignee. Respirable agglomerates of porous carrier particles and micronized drug. 2016.
52. Efficacy and safety of PT003, PT005, and PT001 in subjects with moderate to very severe chronic obstructive pulmonary disease (COPD); (PINNACLE 1) [Internet]. ClinicalTrials.gov. 2017 [cited May 8, 2017]. Available from: https://clinicaltrials.gov/ct2/show/NCT01854645?term=NCT01854645&rank=1.
53. NDA 208294 Approval [Internet]. Food and Drug Administration. 2016 [cited May 8, 2017]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/208294Orig1s000ltr.pdf.
54. Taylor G, Warren S, Dwivedi S, Sommerville M, Mello L, Orevillo C, et al. Gamma scintigraphic pulmonary deposition study of glycopyrronium/formoterol metered dose inhaler formulated using co-suspension delivery technology. Eur J Pharm Sci. 2018;111:450–7.
55. Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. J Asthma. 1994;31(3):193–9.
56. Goodman DE, Israel E, Rosenberg M, Johnston R, Weiss ST, Drazen JM. The influence of age, diagnosis, and gender on proper use of metered-dose inhalers. Am J Respir Crit Care Med. 1994;150(5 Pt 1):1256–61.
57. Myrdal PB, Sheth P, Stein SW. Advances in metered dose inhaler technology: formulation development. AAPS PharmSciTech. 2014;15(2):434–55.
58. Cummings RH, Schultz R, Speck JH, Joshi V, Lechuga-Ballesteros D, Flynn B, et al. Performance advantages of co-suspension formulation technology for manufacturing of metered dose inhalers. Respir Drug Deliv Eur. 2011;2:387–90.
59. Martinez FJ, Rabe KF, Ferguson GT, Fabbri LM, Rennard S, Feldman GJ, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. Chest. 2017;151(2):340–57.
60. Richardson PC, Boss AH. Technosphere insulin technology. Diabetes Technol Ther. 2007;9(Suppl 1):S65–72.
61. Santos Cavaiola T, Edelman S. Inhaled insulin: a breath of fresh air? A review of inhaled insulin. Clin Ther. 2014;36(8):1275–89.
62. Visentin R, Giegerich C, Jager R, Dahmen R, Boss A, Grant M, et al. Improving efficacy of inhaled Technosphere insulin (Afrezza) by postmeal dosing: in-silico clinical trial with the University of Virginia/Padova type 1 diabetes simulator. Diabetes Technol Ther. 2016;18(9):574–85.
63. Angelo R, Rousseau K, Grant M, Leone-Bay A, Richardson P. Technosphere insulin: defining the role of Technosphere particles at the cellular level. J Diabetes Sci Technol. 2009;3(3):545–54.
64. Engstrom JD, Lai ES, Ludher BS, Chen B, Milner TE, Williams RO 3rd, et al. Formation of stable submicron protein particles by thin film freezing. Pharm Res. 2008;25(6):1334–46.
65. Beinborn NA, Lirola HL, Williams RO 3rd. Effect of process variables on morphology and aerodynamic properties of voriconazole formulations produced by thin film freezing. Int J Pharm. 2012;429(1–2):46–57.
66. Watts AB, Wang YB, Johnston KP, Williams RO. Respirable low-density microparticles formed in situ from aerosolized brittle matrices. Pharm Res. 2013;30(3):813–25.
67. Borgstrom L, Olsson B, Thorsson L. Degree of throat deposition can explain the variability in lung deposition of inhaled drugs. J Aerosol Med. 2006;19(4):473–83.
68. Rathbone MJ. Modified-release drug delivery technology. 2nd ed. New York: Informa Healthcare; 2008. p. 563–71.
69. Schuster J, Rubsamen R, Lloyd P, Lloyd J. The AERX aerosol delivery system. Pharm Res. 1997;14(3):354–7.
70. Hindle M, Longest PW. Evaluation of enhanced condensational growth (ECG) for controlled respiratory drug delivery in a mouth-throat and upper tracheobronchial model. Pharm Res. 2010;27(9):1800–11.
71. Longest PW, McLeskey JT Jr, Hindle M. Characterization of nanoaerosol size change during enhanced condensational growth. Aerosol Sci Technol. 2010;44(6):473–83.
72. Hindle M, Longest PW. Condensational growth of combination drug-excipient submicrometer particles for targeted high-efficiency pulmonary delivery: evaluation of formulation and delivery device. J Pharm Pharmacol. 2012;64(9):1254–63.
73. Longest PW, Hindle M. Numerical model to characterize the size increase of combination drug and hygroscopic excipient nanoparticle aerosols. Aerosol Sci Technol. 2011;45(7):884–99.
74. Longest PW, Hindle M. CFD simulations of enhanced condensational growth (ECG) applied to respiratory drug delivery with comparisons to in vitro data. J Aerosol Sci. 2010;41(8):805–20.
75. Tian G, Longest PW, Li X, Hindle M. Targeting aerosol deposition to and within the lung airways using excipient enhanced growth. J Aerosol Med Pulm Drug Deliv. 2013;26(5):248–65.
76. Longest PW, Xi J, Hindle M, inventors; Virginia Commonwealth University, assignee. Effective delivery of nanoparticles and micrometer-sized pharmaceutical aerosols to the lung through enhanced condensational growth. 2009.
77. Son Y-J, Worth Longest P, Hindle M. Aerosolization characteristics of dry powder inhaler formulations for the excipient enhanced growth (EEG) application: effect of spray drying process conditions on aerosol performance. Int J Pharm. 2013;443(1–2):137–45.
78. Walenga RL, Longest PW, Kaviratna A, Hindle M. Aerosol drug delivery during noninvasive positive pressure ventilation:

effects of intersubject variability and excipient enhanced growth. J Aerosol Med Pulm Drug Deliv. 2017;30(3):190–205.
79. Farkas D, Hindle M, Longest PW. Application of an inline dry powder inhaler to deliver high dose pharmaceutical aerosols during low flow nasal cannula therapy. Int J Pharm. 2018;546(1–2):1–9.
80. Mack P, Tully J, Garcia A, Maynor BW. Microfabricated itraconazole for enhanced respiratory delivery and dissolution. Respir Drug Deliv. 2012;2:569–72.
81. Maynor BW. 21st century particle engineering: particle design, manufacture, and scale-up of PRINT® technology. Respir Drug Deliv. 2018;1:211–20.
82. Maynor BW, Andres G, Duong H, Mark P. Microfabricated, shape-specific particles and engineered aerosols for efficient aerosol delivery to the lung. Respir Drug Deliv. 2010;2:619–22.
83. Mack P, Tully J, Herlihy KP, Farrer B, Sprague J, Maynor BW. Formulation and in vivo evaluation of treprostinil dry powder for inhalation, fabricated using the PRINT® particle technology. Respir Drug Deliv. 2014;2:473–6.
84. Galloway A, Murphy A, DeSimone J, Di J, Herrmann J, Hunter M, et al. Development of a nanoparticle-based influenza vaccine using the PRINT technology. Nanomedicine. 2013;9(4):523–31.
85. Du P, Du J, Smyth HD. Evaluation of granulated lactose as a carrier for DPI formulations: effect of drug loading. Respir Drug Deliv. 2014;3:743–6.
86. Raula J, Thielmann F, Naderi M, Lehto V-P, Kauppinen EI. Investigations on particle surface characteristics vs. dispersion behaviour of L-leucine coated carrier-free inhalable powders. Int J Pharm. 2010;385(1–2):79–85.
87. Du P, Du J, Smyth HD. Evaluation of granulated lactose as a carrier for dry powder inhaler formulations 2: effect of drugs and drug loading. J Pharm Sci. 2017;106(1):366–76.
88. Du P, Du J, Smyth HD. Evaluation of granulated lactose as a carrier for DPI formulations 1: effect of granule size. AAPS PharmSciTech. 2014;15(6):1417–28.
89. Sou T, Orlando L, McIntosh MP, Kaminskas LM, Morton DA. Investigating the interactions of amino acid components on a mannitol-based spray-dried powder formulation for pulmonary delivery: a design of experiment approach. Int J Pharm. 2011;421(2):220–9.
90. Lord J. AeroVancTM: a novel dry powder inhaler for the treatment of methicillin-resistant Staphylococcus aureus infection in cystic fibrosis patients. Respir Drug Deliv. 2014;3:563–8.
91. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52(3):e18–55.
92. A study of AeroVanc for the treatment of MRSA infection in CF patients [Internet]. ClinicalTrials.gov. 2017 [cited June 13, 2018]. Available from: https://clinicaltrials.gov/ct2/show/NCT03181932.
93. Chvatal A, Farkas A, Balashazy I, Szabo-Revesz P, Ambrus R. Aerodynamic properties and in silico deposition of meloxicam potassium incorporated in a carrier-free DPI pulmonary system. Int J Pharm. 2017;520(1–2):70–8.
94. Manzanedo D, Brande M, Kramer SR, Yee LW, DeHaan WH, Clarke R, et al. Formulation characterization of a novel levofloxacin pulmonary dry powder drug delivery technology. Respir Drug Deliv. 2012;3:713–6.
95. Lawlor C, Clarke R, Sung JC. Development of an iSPERSE based platform for the delivery of macromolecules via dry powder formulations. Respir Drug Deliv. 2012;3:709–12.
96. Lipp MM, Sung JC, inventors. Pulmatrix, Inc, assignee. Respirably dry powder comprising calcium lactate, sodium chloride and leucine. United States 2015 Jul 23, 2015.
97. Kwok PCL, Chan H-K. Advances in pulmonary drug delivery. New York: Routledge; 2017.
98. Zhou QT, Qu L, Gengenbach T, Denman JA, Larson I, Stewart PJ, et al. Investigation of the extent of surface coating via mechanofusion with varying additive levels and the influences on bulk powder flow properties. Int J Pharm. 2011;413(1–2):36–43.
99. Zhou QT, Qu L, Larson I, Stewart PJ, Morton DAV. Improving aerosolization of drug powders by reducing powder intrinsic cohesion via a mechanical dry coating approach. Int J Pharm. 2010;394(1–2):50–9.
100. Farr SJ, Rowe AM, Rubsamen R, Taylor G. Aerosol deposition in the human lung following administration from a microprocessor controlled pressurised metered dose inhaler. Thorax. 1995;50(6):639–44.
101. Gonda I, Schuster JA, Rubsamen RM, Lloyd P, Cipolla D, Farr SJ. Inhalation delivery systems with compliance and disease management capabilities. J Control Release. 1998;53(1–3):269–74.
102. Digital Dose Inhaler Market analysis and segment forecasts to 2024. San Francisco: Grand View Research, Inc.; 2016.
103. Global smart inhaler technology market 2018–2022. Dublin 8, Ireland: Research and Markets; 2018 Feburary 2018.
104. Smart inhalers market research report—global forecast to 2022. Pune, India: Market Research Future; 2017 March, 2017.
105. Merchant RK, Inamdar R, Quade RC. Effectiveness of population health management using the propeller health asthma platform: a randomized clinical trial. J Allergy Clin Immunol Pract. 2016;4(3):455–63.
106. Yan W. Toward better management for asthma: from smart inhalers to injections to wearables, researchers are finding new ways to improve asthma treatment. IEEE Pulse. 2018;9(1):28–33.
107. 3M. 3M unveils intelligent inhaler designed to help control spiraling costs of respiratory disease 2016 [updated April 19, 2016. Available from: http://www.3m.com/3M/en_US/drug-delivery-systems-us/resources/news/news-detail/?storyid=7bb6559f-bb24-4a1a-a4fe-628b724a2915.
108. Glusker M, Axford G, Le J, Lin J, Maltz DS, Paterson D, et al. USSC-03: a modular breath-actuated multi-dose dry powder inhaler system with Telehealth capability. Respir Drug Deliv. 2016;3:449–54.
109. Kim MS, Henderson KA, Van Sickle D. Using connected devices to monitor inhaler use in the real world. Respir Drug Deliv. 2016;1:37–44.
110. Van Sickle D, Maenner MJ, Barrett M, Marcus JE. Monitoring and improving compliance and asthma control: mapping inhaler use for feedback to patients, physicians and payers. Respir Drug Deliv Eur. 2013;1:119–30.
111. 510(k) Premarket Notification Reciprocal Labs Corporation Asthmapolis System [Internet]. U.S. Food and Drug Administration. 2012 [cited Jun. 25, 2018]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf12/K121609.pdf.
112. Propeller Health enters into collaboration to connect Breezhaler™ devices to the propeller platform [press release]. Feb. 8, 2017 2017.
113. Barrett M, Combs V, Su JG, Henderson K, Tuffli M, Collaborative AIRL, et al. AIR Louisville: addressing asthma with technology, crowdsourcing, cross-sector collaboration, and policy. Health Aff (Millwood). 2018;37(4):525–34.
114. Adherium launches the Hailie™ global brand to connect people with asthma and COPD to better care [press release]. May 17, 2018.
115. Perez C. Smart inhalers and the future of respiratory health management. 2015 [updated Oct., 2015; cited 2018 May 1]; Available from: http://alliedweb.s3.amazonaws.com/rtmagazi/diged/201510/html5/index.html.
116. Adherium. Nexus6 receives FDA clearance for latest smartinhaler 2014 [cited Nov 9, 2016]; Available from: http://www.smartinhaler.com/nexus6-receives-fda-clearance-for-latest-smartinhaler/.
117. Teva reinforces leadership position in respiratory with acquisition of Gecko Health Innovations 2015 [cited Nov 9, 2017]; Available from: http://www.tevapharm.com/news/teva_reinforces_leadership_position_in_respiratory_with_acquisition_of_gecko_health_innovations_09_15.aspx.
118. Kikidis D, Konstantinos V, Tzovaras D, Usmani OS. The digital asthma patient: the history and future of inhaler based health monitoring devices. J Aerosol Med Pulm Drug Deliv. 2016;29(3):219–32.
119. Specifications. Gecko Health Innovations, Inc; [cited May 9, 2017]; Available from: https://www.caretrx.com/.
120. Milton-Edwards M, Chrystyn H, Morrison MS, Weitzel DE, inventors. Inhalation monitoring system and method. United States 2016.

121. RDD 2016 In Review 2016 [cited May 9, 2017]; Available from: http://www.rddonline.com/rdd/rdd.php?id=12.
122. 3M unveils intelligent inhaler designed to help control spiraling costs of respiratory disease 2016 [cited May 9, 2018]; Available from: http://news.3m.com/press-release/company-english/3m-unveils-intelligent-inhaler-designed-help-control-spiraling-costs-r.
123. Harm C. There's a digital health app for that!: highlighting a sampling of new digital health devices that span the wide focus terrain in health technology.
124. Systems MDD. Introducing the 3M intelligent control inhaler. St. Paul, MN2017 [cited May 9, 2017]; Available from: http://multimedia.3m.com/mws/media/1204262O/3mtm-intelligent-control-inhaler-sell-sheet.pdf.
125. Serafin C, Maltz DS, Glusker M, Lin J, Weers JG. Aspirations for usability: successful including human factors in the design of the USSC-03 inhaler. Respir Drug Deliv. 2016;3:477–80.
126. Colthorpe P, Pavkov R, Rozenman Y, Humby C. Adding electronics to the Breezhaler®: satisfying the needs of patients and regulators. Respir Drug Deliv. 2018;1:71–80.
127. Chrystyn H, Safioti G, Calderon E, Buck D, Forrestal J, Milton-Edwards M, et al. In vitro assessment of a novel integrated electronic multidose dry powder inhaler. Respir Drug Deliv. 2018;1(2):527–32.
128. George M. Adherence in asthma and COPD: new strategies for an old problem. Respir Care. 2018;63(6):818–31.
129. Rackley J. Smart inhalers: pros and cons HealthCentral: Remedy Health Media, LLC; 2017 [updated May 12, 2017. Available from: https://www.healthcentral.com/article/smart-inhalers-pros-and-cons.
130. Merchant R, Inamdar R, Henderson K, Barrett M, Su JG, Riley J, et al. Digital health intervention for asthma: patient-reported value and usability. JMIR Mhealth Uhealth. 2018;6(6):e133.
131. Morton RW, Elphick HE, Rigby AS, Daw WJ, King DA, Smith LJ, et al. STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. Thorax. 2017;72(4):347–54.
132. Nelson R. The excessive waste of prescription drugs. Am J Nurs. 2015;115(6):19–20.
133. Potera C. Drugged drinking water. Environ Health Perspect. 2000;108(10):A446.
134. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. Am J Respir Crit Care Med. 2014;189(8):975–82.
135. Bell JH, Hartley PS, Cox JS. Dry powder aerosols. I. A new powder inhalation device. J Pharm Sci. 1971;60(10):1559–64.
136. Berkenfeld K, Lamprecht A, McConville JT. Devices for dry powder drug delivery to the lung. AAPS PharmSciTech. 2015;16(3):479–90.
137. Weers J, Clark A. The impact of inspiratory flow rate on drug delivery to the lungs with dry powder inhalers. Pharm Res. 2017;34(3):507–28.
138. Patterson R, Grammer LC, Greenberger PA. Patterson's allergic diseases. 7th ed. Baltimore: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009. xxi, 713 p.
139. Olsson B, Borgstrom L, Asking L, Bondesson E. Effect of inlet throat on the correlation between measured fine particle dose and lung deposition. Respir Drug Deliv. 1996;1:273–82.
140. Ung K, Rao N, Weers J, Clark A, Chan HK. In vitro assessment of dose delivery performance of dry powders for inhalation. Aerosol Sci Technol. 2014;48(10):1099–110.
141. Grant AC, Walker R, Hamilton M, Garrill K. The ELLIPTA(R) dry powder inhaler: design, functionality, in vitro dosing performance and critical task compliance by patients and caregivers. J Aerosol Med Pulm Drug Deliv. 2015;28(6):474–85.
142. Collison KA, Patel P, Preece AF, Stanford RH, Sharma RK, Feldman G. A randomized clinical trial comparing the ELLIPTA and HandiHaler dry powder inhalers in patients with COPD: inhaler-specific attributes and overall patient preference. COPD. 2018;15(1):46–50.
143. van der Palen J, Thomas M, Chrystyn H, Sharma RK, van der Valk PD, Goosens M, et al. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices. NPJ Prim Care Respir Med. 2016;26:16079.
144. Yun Kirby S, Zhu C-Q, Kerwin EM, Stanford RH, Georges G. A preference study of two placebo dry powder inhalers in adults with COPD: ELLIPTA dry powder inhaler (DPI) versus DISKUS DPI. COPD. 2016;13(2):167–75.
145. Anhang Price R, Elliott MN, Zaslavsky AM, Hays RD, Lehrman WG, Rybowski L, et al. Examining the role of patient experience surveys in measuring health care quality. Med Care Res Rev. 2014;71(5):522–54.
146. Welch MJ. Pharmacokinetics, pharmacodynamics, and clinical efficacy of albuterol RespiClick() dry-powder inhaler in the treatment of asthma. Expert Opin Drug Metab Toxicol. 2016;12(9):1109–19.
147. Azouz W, Chetcuti P, Hosker H, Saralaya D, Chrystyn H. Inhalation characteristics of asthma patients, COPD patients and healthy volunteers with the Spiromax and Turbuhaler devices: a randomised, cross-over study. BMC Pulm Med. 2015;15:47.
148. FDA Label, Proair Respiclick (albuterol sulfate) inhalation powder, for oral inhalation use: FDA; 2016 [cited May 9, 2017]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205636s006lbl.pdf.
149. Mendes PJ, Goncalves A, Santos P, Villax P. TwinCaps: developing an in-vitro equivalent DPI. Respir Drug Deliv Eur. 2009;2:305–8.
150. Fernandes JV, Lopes IS, Santos B, Neves F, Winters C. Performance optimization in early DPI development: enabling high dosage drug delivery to the lungs through orifice-based aerosolization. Respir Drug Deliv Eur. 2015;2:311–4.
151. Williams G, Grosjean B. Twister®: a new spin for capsule dry powder inhalers. Respir Drug Deliv. 2016:221–4.
152. AptarGroup. Twister [cited May 9, 2017]; Available from: https://pharma.aptar.com/en-us/dispensing-solutions/twisterr.html.
153. Bischofberger JE, Rhima CE, Tibbatts J, Christie E, Ahern D, Chhabildas VS, et al. A study on the inspiratory flow rate and power required to trigger flutiform® k-haler®, Qvar® Easi-Breathe®, and Fostair® NEXThaler® breath actuated inhalers. Respir Drug Deliv. 2018;2:363–8.
154. Buttini F, Brambilla G, Copelli D, Sisti V, Balducci AG, Bettini R, et al. Effect of flow rate on in vitro aerodynamic performance of NEXThaler((R)) in comparison with Diskus((R)) and Turbohaler((R)) dry powder inhalers. J Aerosol Med Pulm Drug Deliv. 2016;29(2):167–78.
155. FDA Label, Instructions for use TOBI Podhaler [Internet]. 2016 [cited May 9, 2016]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/201688s008lbl.pdf.
156. Zhu B, Padroni M, Colombo G, Phillips G, Crapper J, Young PM, et al. The development of a single-use, capsule-free multi-breath tobramycin dry powder inhaler for the treatment of cystic fibrosis. Int J Pharm. 2016;514(2):392–8.
157. Young PM, Crapper J, Philips G, Sharma K, Chan H-K, Traini D. Overcoming dose limitations using the orbital() multi-breath dry powder inhaler. J Aerosol Med Pulm Drug Deliv. 2014;27(2):138–47.
158. de Boer AH, Hagedoorn P, Woolhouse R, Wynn E. Computational fluid dynamics (CFD) assisted performance evaluation of the Twincer disposable high-dose dry powder inhaler. J Pharm Pharmacol. 2012;64(9):1316–25.
159. Fernandes JV, Enes NR, Winters C. From TwinCaps® to TwinMax™: optimizing a disposable inhaler for high dosage applications through CFD. Respir Drug Deliv. 2016;2:345–50.
160. Haynes A, Geller D, Weers J, Ament B, Pavkov R, Malcolmson R, et al. Inhalation of tobramycin using simulated cystic fibrosis patient profiles. Pediatr Pulmonol. 2016;51(11):1159–67.
161. Curtis RM, Donovan MJ, Smyth HDC, inventors. Inhaler to deliver substances for prophylaxis or prevention of disease or injury caused by the inhalation of biological or chemical agents. United States; 2013.
162. Rubin BK, Williams RW. Emerging aerosol drug delivery strategies: from bench to clinic. Adv Drug Deliv Rev. 2014;75:141–8.
163. Gardenhire DS, Ari A, Hess D, Myers TR. A guide to aerosol delivery devices for respiratory therapists. American Association for Respiratory Care; 2013.

164. Rau JL, Ari A, Restrepo RD. Performance comparison of nebulizer designs: constant-output, breath-enhanced, and dosimetric. Respir Care. 2004;49(2):174–9.
165. Rubin BK, Fink JB. Treatment delivery systems. In: Cstro M, Kraft M, editors. Clinical asthma. Elsevier; 2008. p. 303–12.
166. Dhand R. Nebulizers that use a vibrating mesh or plate with multiple apertures to generate aerosol. Respir Care. 2002;47(12):1406–16 discussion 16-8.
167. Skaria S, Smaldone GC. Omron NE U22: comparison between vibrating mesh and jet nebulizer. J Aerosol Med Pulm Drug Deliv. 2010;23(3):173–80.
168. Hsiao S-C, Chou C-W, Tsai T-K, Lu C-W, Hsu C-C, Li S-W, et al. A novel contact-triggered vibrating mesh nebulizer: aerodynamic performance and drug distribution of suspension drug delivered with MicroBase μSMI. Respir Drug Deliv. 2018;1:459–62.
169. Xu H, inventor; Stamford Devices Ltd., assignee. Photodefined aperture plate and method for producing the same. USA 2017 Aug 1, 2017.
170. Fink J, MacLoughlan R, Telfer C, Clark AR. Developing inhaled drugs for critically ill patients: a platform for all ages. Respir Drug Deliv. 2016;2:249–52.
171. Ari A. Jet, ultrasonic, and mesh nebulizers: an evaluation of nebulizers for better clinical outcomes. Eurasian J Pulmonol. 2014;16:1–7.
172. Kelkar MS, Dalby RN. Formulation of suspension-type pressurized metered dose inhalers using effervescent aerosol technology. Respir Drug Deliv Eur. 2015;2:493–6.
173. Addington W, Miller SP, Phelipa MM, Stephens RE, inventors. Pneumoflex Systems LLC, assignee. Nebulizer having horizontal venturi. United States 2014.
174. Addington WR, Miller SP, Warren J. Optimization of jet nebulizers: horizontal venturi nebulization. Respir Drug Deliv Asia. 2016;1:251-4.
175. Potter G, Tokranova N, Rastegar A, Cstracane J. Design, fabrication, and testing of surface acoustic wave devices for semiconductor cleaning applications. Microelectron Eng. 2016;162:100–4.
176. Li C, Guan G, Zhang F, Nabi G, Wang RK, Huang Z. Laser induced surface acoustic wave combined with phase sensitive optical coherence tomography for superficial tissue characterization: a solution for practical application. Biomed Opt Express. 2014;5(5):1403–19.
177. Yeo LY, Rezk AR. Next generation nebulization platform for inhaled macromolecular therapeutics. Respir Drug Deliv Asia. 2016;1:25–32.
178. Kurosawa M, Watanabe T, Futami A, Higuchi T. Surface acoustic wave atomizer. Sensors Actuators A. 1995;50:69–74.
179. Qi A, Yeo LY, Friend JR. Interfacial destabilization and atomization driven by surface acoustinc waves. Phys Fluids. 2008;20(7):074103.
180. Hickey AJ. Pharmaceutical inhalation aerosol technology. 2nd ed. New York: M. Dekker; 2004. xv, 603 p. p
181. Wang Y, Rezk AR, Khara JS, Yeo LY, Ee PLR. Stability and efficacy of synthetic cationic antimicrobial peptides nebulized using high frequency acoustic waves. Biomicrofluidics. 2016;10(3):034115.
182. NDA 21747 Approval [Internet]. Food and Drug Administration. 2011 [cited May 9, 2018]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021747s000ltr.pdf.
183. Patton JS, Porter L. Re-thinking inhaled Insulin's role in the global challenge to treat diabetes. Respir Drug Deliv Eur. 2015;1:49–58.
184. Anderson P. Use of Respimat soft mist inhaler in COPD patients. Int J Chron Obstruct Pulmon Dis. 2006;1(3):251–9.
185. Fink J, Molloy L, Patton JS. Human factors driving design to superior liquid inhaler performance. Respir Drug Deliv. 2016;2:295–8.
186. Dose-response and variability of inhaled insulin in type 2 diabetes (Samba-02) [Internet]. ClinicalTrials.gov. 2016 [cited May 9, 2017]. Available from: https://clinicaltrials.gov/ct2/show/NCT02716610?term=insulin&spons=dance&rank=2.
187. Nicola M, Elberry A, Sayed O, Hussein R, Saeed H, Abdelrahim M. The impact of adding a training device to familiar counselling on inhalation technique and pulmonary function of asthmatics. Adv Ther. 2018;35(7):1049–58.
188. Vehring R, Hartman MS, Schultz RK, Joshi V, Smmerville M, Cummings H, et al. Glycopyrrolate and formoterol fumarate monotherapy and combination metered dose inhalers with high dose uniformity and stable aerosol properties. Am J Respir Crit Care Med. 2010;181(Poster Abstract):A4452.
189. Zhou QT, Tang P, Leung SS, Chan JG, Chan HK. Emerging inhalation aerosol devices and strategies: where are we headed? Adv Drug Deliv Rev. 2014;75:3–17.
190. Corr S, Noakes TJ, inventors. Composition comprising salbutamol sulphate 2014.
191. Gupta A, Stein SW, Myrdal PB. Balancing ethanol cosolvent concentration with product performance in 134a-based pressurized metered dose inhalers. J Aerosol Med. 2003;16(2):167–74.
192. Corr S, Noakes TJ, inventors. Compositions comprising salbutamol sulphate 2013.
193. Corr S, Noakes T. Compatibility of P152a with pressurized metered dose inhaler device materials. Respir Drug Deliv. 2018;1(2):455–8.
194. Corr S, Noakes T. Pressurized metered dose inhaler propellants: going forward. Respir Drug Deliv. 2017;2:255–8.
195. Keller M, Herzog K, inventors; Jago Research AG, assignee. Medical Aerosol Formulations. United States; 2002.
196. Kelkar MS, Dalby RN. Effervescent aerosols: a novel formulation technology for pressurized metered dose inhalers. Respir Drug Deliv. 2014;3:669–72.
197. Kelkar MS, Dalby RN. Plume geometry evaluation of solution-type metered dose inhalers formulated using effervescent aerosol technology. Respir Drug Deliv. 2016;3:579–82.