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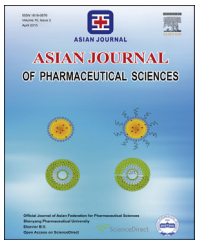

Review

Practical, regulatory and clinical considerations for development of inhalation drug products

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ABSTRACT

The formulation and device collectively constitute an inhalation drug product. Development of inhaled drugs must consider the compatibility between formulation and device in order to achieve the intended pharmaceutical performance and usability of the product to improve patient compliance with treatment instruction. From the points of formulation, device and patient use, this article summarizes the inhalation drugs, including pressurized metered dose inhaler (pMDI), dry powder inhaler (DPI), and nebulizer that are currently available in the US and UK markets. It also discusses the practical considerations for the development of inhalers and provides an update on the corresponding regulations of the FDA (U.S. Food and Drug Administration) and the EMA (European Medicines Agency).

1. Introduction

Respiratory drug delivery has strong interest in the pharmaceutical field from both industries and academics, due to the fact that inhalation therapy not only has been widely accepted for localized treatment for pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD), but also as an alternative route for systemic drug administration for diseases such as diabetes [1]. For local activities, the orally inhaled drugs are delivered directly to the site of action in the lung, providing fast onset of action (within 5 minutes) [2]. A sustained activity can also be achieved by utilizing long-acting drugs (e.g., salmeterol and tiotropium) and/or by modifying formulation technology to better meet the clinical needs and patient compliance [3,4]. In the case of systemic drug delivery via inhalation, the lung provides the advantage of large alveolar epithelial absorption area with low enzymatic activity, which makes it a suitable route for biological products such as insulin. Drugs absorbed through the lung can also avoid first-pass metabolism and have thus shown an improved bioavailability.

Inhalation drug products are commonly classified into three categories: pressurized metered dose inhaler (pMDI), dry powder inhaler (DPI) and nebulizer. All these inhalation drug products are a combination of formulation and device, with patient use as the target consideration (Fig. 1). The formulation is designed

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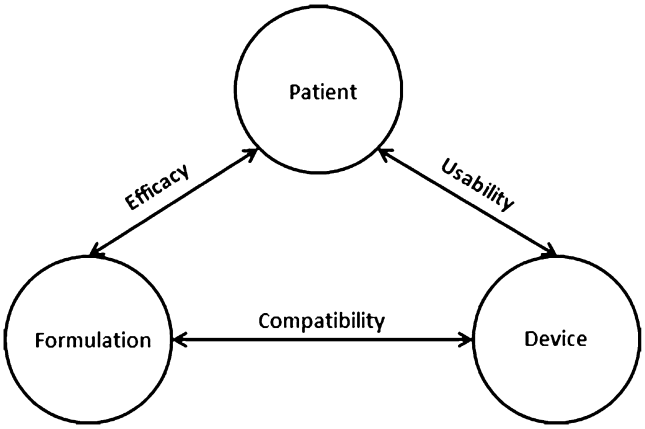

Fig. 1 – Overall considerations for development of inhalation drug products.

to provide intended efficacy for patients, and to achieve this goal, it needs to be compatible and works together with a device. An inhalation product should be able to provide consistent dose content, along with suitable aerodynamic particle size distribution, to ensure that the drugs can be efficiently delivered to the target sites in the lung. A well-designed inhaler must also consider its usability for patients' use in terms of features such as robustness, ease of use, portability, and suitability for all ages in order to achieve good patient compliance with the technique instructions.

The development of an inhalation product must take into account of the following factors: (a) type of drugs being delivered to the lung, such as local or systemic action, chemical or biological drug, and dose and frequency for patient use; (b) physico-chemical properties of the drug substance, such as solubility profile, particle size, morphology and density, as these determine the formulation development; (c) type of formulation (e.g., dry powder, propellant driven liquid, or aqueous inhalation formulation) being selected to deliver the drug; (d) device design for compatibility with the formulation to be suitable for the targeted patient population.

Each type of inhaler has its specific formulation, device and clinical advantages. The inhalation products currently available in the US and UK markets are summarized in Tables 1–3 for pMDIs, DPIs and nebulizers, respectively. Based on these product's formulation and device information, this article discusses the practical strategies and clinical considerations for the development of each type of inhalers and provides an update for the regulatory guidelines issued by the FDA and EMA for these inhalers, specifically for generic inhalation products. Any new technology and new inhalation drug that are still under the investigation phases will be briefly mentioned.

2. pMDIs

2.1. *Formulation*

pMDIs are either suspension or solution based formulation of drug in propellants. The traditional chlorofluorocarbon (CFC) propellants, which have previously been used in pMDIs for decades, were banned by the Montreal Protocol (1989) due to their ozone depletion effect. The hydrofluoroalkanes (HFA-134a and HFA 227) were selected as alternative propellants. This propellant transition for pMDIs is almost complete in western countries [5]. All researches for pMDI development are referred to the landmark publication by Vervaet and Byron to further understand the drug–surfactant–propellant interactions in the HFA formulations. That article systemically presented an overview of the present state-of-the-art with respect to the physico-chemical characteristics of HFA and HFA–ethanol blends, drug substance properties that need to be considered for formulation development, and surfactant behaviors in the pMDI formulations [6]. The important properties of the drug substance such as solubility profile, particle size, morphology and density, need to be characterized first, as these parameters will influence the formulation decision (solution or suspension) and drug micronization method selection [7]. As for the surfactants in suspension formulations, such as oleic acid in Proventil and polyethylene glycol (PEG) 1000 in Symbicort, they serve to lubricate the valves to improve the drug delivery efficiency and dose uniformity. However, the surfactants previously soluble in the CFC formulations, especially the surfactants with low hydrophilic-lipophilic balance (HLB) values, show decreased solubility in the HFA propellants. More hydrophilic surfactants with higher HLB values, such as PEG, tend to dissolve more in HFAs [6]. Co-solvents such as anhydrous ethanol may also needed to help improve the solubilization of the surfactants in the HFA formulations, but the ethanol content in pMDI suspension formulations should be minimized to avoid the dissolution of drug. This is because the partly soluble micronized drug may lead to crystal growth (**Ostwald ripening:** a phenomenon in suspension that describes the change of an inhomogeneous structure over time, i.e., small crystals or particles dissolve, and redeposit onto larger crystals or particles), resulting to reduced drug delivery consistency and increased particle size distribution [6]. Ethanol can also be used to increase the solubility of drug to form a solution formulation, such as Qvar (Beclomethasone dipropionate solution formulation). Such a solution formulation generates significantly smaller particle size compared to the typical suspension formulation, leading to reduced oropharyngeal deposition and improved lung deposition [8]. Having said that, the ethanol content in solution formulations must be balanced, as higher ethanol concentration can lead to decreased fine particle fraction, mainly due to the increase in initial atomized droplet size that subsequently affects solvent evaporation [9,10]. The chemical stability of drug could also be an issue for solution formulations [11,12]. In Atrovent, a solution formulation of ipratropium bromide, water and citric acid are added to improve the drug chemical stability. Citric acid acts as an organic acid, provides stability against degradation or decomposition of the medicament resulting largely from interaction of the medicament with the cosolvent and/or water present in the solution formulation [13]. The physical stability such as drug particle agglomeration and adsorption is a challenge to formulate a suspension formulation. Suspending agents, such as povidone K25 in Symbicort, are used to improve the drug particle suspension [14]. Suspending agents can increase suspension viscosity and/or provide steric hindrance to aid the stabilization of microparticles in the pMDI

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Table 1 – The pressurized metered dose inhalers in the US & UK markets.

Indications	APIs	Products	Manufacturer	Formulation	Device
Asthma and COPD	Albuterol sulfate	Proair	Teva	Drug, HFA-134a, Ethanol (Suspension)	Valve, Canister, Acuator
		Proventil	Merck	Drug, HFA-134a, Ethanol, Oleic acid (Suspension)	Valve, Canister, Acuator
		Ventolin	GlaxoSmithKline	Drug, HFA-134a (Suspension)	Valve, Canister, Acuator with dose counter
	Salbutamol xinafoate	AirSalb	Sandoz	Drug, HFA-134a, Ethanol, Oleic acid (Suspension)	Valve, Canister, Acuator
	Levalbuterol tartrate	Xopenex	Sunovion	Drug, HFA-134a, Ethanol, Oleic acid (Suspension)	Valve, Canister, Acuator
	Formoterol fumarate	Atimos Modulite	Chiesi	Drug, HFA-134a, Ethanol, Hydrochloric acid (Solution)	Valve, Canister, Acuator
	Ipratropium bromide	Atrovent	Boehringer Ingelheim	Drug, HFA-134a, Water, Ethanol, Citric acid (Solution)	Valve, Canister, Acuator with dose counter
	Sodium cromoglycate	Intal	Sanofi Aventis	Drug, HFA-227, Polyvidone K30, Polyethylene glycol 600 (Suspension)	Valve, Canister, Acuator
	Beclomethasone dipropionate	Clenil Modulite	Chiesi	Drug, HFA-134a, Ethanol, Glycerol (Solution)	Valve, Canister, Acuator
		Qvar	Teva	Drug,HFA-134a, Ethanol (Solution)	Valve, Canister, Acuator
		Qvar Autohaler	3M	Drug,HFA-134a, Ethanol (Solution)	Valve, Canister, Breath-activated Acuator
	Ciclesonide	Alvesco	Takeda	Drug,HFA-134a, Ethanol (Solution)	Valve, Canister, Acuator with dose counter
	Flunisolide	Aerospan	Meda	Drug,HFA-134a, Ethanol (Solution)	Valve, Canister, Acuator with spacer
	Fluticasone propionate	Flovent	GlaxoSmithKline	Drug,HFA-134a (Suspension)	Valve, Canister, Acuator with dose counter
	Beclomethasone dipropionate + Formoterol fumarate	Fostair	Chiesi	Drug, HFA-134a, Ethanol, Hydrochloric acid (Solution)	Valve, Canister, Acuator
	Budesonide + Formoterol fumarate	Symbicort	AstraZeneca	Drug, HFA 227, Povidone K25, Polyethylene glycol 1000 (Suspension)	Valve, Canister, Acuator with dose counter
	Fluticasone propionate + Formoterol fumarate	Flutiform	Napp	Drug, HFA-227, Sodium cromoglicate, Ethanol (Suspension)	Valve, Canister, Acuator with dose counter
	Fluticasone propionate + Salmeterol xinafoate	Advair	GlaxoSmithKline	Drug,HFA-134a (Suspension)	Valve, Canister, Acuator with dose counter
	Mometasone furoate + Formoterol fumarate	Dulera	Merck	Drug, HFA-227, Ethanol, Oleic acid (Suspension)	Valve, Canister, Acuator with dose counter

formulations [15,16]. Moisture ingress could also damage the stability of suspension formulations [17]. In summary, to formulate a stable pMDI formulation, the physico-chemical property, such as solubility, particle size, morphology and density of drug substance, type of surfactants and/or suspending agents for stabilizing the formulation, use of ethanol as co-solvent for improving the solubility of surfactants and drug, should be systemically studied [6,18].

2.2. *Container closure system*

The physical and chemical compatibility between pMDI formulation and container closure system components (including metering valve, canister and actuator) is critical for a successful development of pMDI. The target dose to be delivered is determined by the combination of drug concentration and the chamber volume of the metering valve (typically 25–100 μL). The valve materials may influence the drug's physical uptake, drug chemical degradation, moisture ingress and leak rate [17,19]. The extractable and leachable profiles of the valve materials must also be thoroughly investigated, and the leachables from these materials into the pMDI formulations should be closely monitored during product development [7,20]. The pMDI containers are normally **aluminum canisters, which could cause drug loss** through adsorption onto the canister and catalyze the chemical degradation [12,21,22]. **Inner wall coated containers** may be used to replace the aluminum canisters. The **common coatings** are epoxy-phenolic polymer (Epoxy), polytetrafluoroethylene (PTFE), perfluorinated ethylene propylene copolymer (FEP), perfluoroalkoxyalkane polymer (PFA), and polyethersulfone (PES) [22,23]. Appropriate size containers should also be selected based on the actual formulation

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Table 2 – The dry powder inhalers in the US & UK markets.

Indications	APIs	Products	Manufacturer	Formulation	Device type
Asthma and COPD	Albuterol sulfate	ProAir Respiclick	Teva	Drug, Lactose monohyrdrate	Passive, Reservoir, Multiple dose
	Salbutamol sulfate	Pulvinal Salbutamol	Chiesi	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
		Easyhaler Salbutamol Sulfate	Orion	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
	Terbutaline sulfate	Bricanyl Turbohaler	AstraZeneca	Drug	Passive, Reservoir, Multiple dose
	Salmeterol xinafoate	Serevent Diskus	GlaxoSmithKline	Drug, Lactose monohydrate	Passive, Blister strip, Multiple dose
	Formoterol fumarate	Foradil Aerolizer	Novartis	Drug, Lactose	Passive, Capsule, Single dose
		Foradil Certihaler	Novartis	Drug, Lactose monohydrate, Magnesium stearate	Passive, Reservoir, Multiple dose
		Oxis Turbohaler	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
		Easyhaler Formoterol	Orion	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
	Indacaterol maleate	Arcapta Neohaler	Novartis	Drug, Lactose monohydrate	Passive, Capsule, Single dose
		Onbrez Breezhaler	Novartis	Drug, Lactose monohydrate	Passive, Capsule, Single dose
	Tiotropium bromide	Spiriva Handihaler	Boehringer Ingelheim	Drug, Lactose monohydrate	Passive, Capsule, Single dose
	Aclidinium bromide	Tudorza Pressair	Forest	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
		Eklira Genuair	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
	Glycopyrronium bromide	Seebri Breezhaler	Novartis	Drug, Lactose monohydrate, Magnesium stearate	Passive, Capsule, Single dose
	Umeclidinium	Incruse Ellipta	GlaxoSmithKline	Drug, Lactose monohydrate, Magnesium stearate	Passive, Blister strip, Multi-unit dose
	Budesonide	Easyhaler Budesonide	Orion	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
		Pulmicort Flexhaler	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
		Pulmicort Turbuhaler	AstraZeneca	Drug	Passive, Reservoir, Multiple dose
	Mometasone furoate	Asmanex Twisthaler	Merck	Drug, Lactose Anhydrate	Passive, Reservoir, Multiple dose
	Beclomethasone dipropionate	Pulvinal Beclometasone Dipropionate	Chiesi	Drug, Lactose monohydrate, Magnesium stearate	Passive, Reservoir, Multiple dose
		Easyhaler Beclometasone	Orion	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
	Fluticasone propionate	Flovent Diskus	GlaxoSmithKline	Drug, Lactose monohydrate	Passive, Blister strip, Multi-unit dose
	Fluticasone furoate	Arnuity Ellipta	GlaxoSmithKline	Drug, Lactose monohydrate	Passive, Blister strip, Multi-unit dose
	Beclomethasone dipropionate + Formoterol fumarate	Fostair Nexthaler	Chiesi	Drug, Lactose monohydrate, Magnesium stearate	Passive, Reservoir, Multiple dose
	Budesonide + Formoterol fumarate	Symbicort Turbohaler	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
		DuoResp Spiromax	Teva	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
	Fluticasone furoate + Vilanterol	Breo Ellipta	GlaxoSmithKline	Drug, Lactose monohydrate, Magnesium stearate	Passive, Blister strip, Multi-unit dose
	Fluticasone propionate + Salmeterol	Advair Diskus	GlaxoSmithKline	Drug, Lactose monohydrate	Passive, Blister strip, Multi-unit dose
	Umeclidinium + Vilanterol	Anoro Ellipta	GlaxoSmithKline	Drug, Lactose monohydrate, Magnesium stearate	Passive, Blister strip, Multi-unit dose
	Glycopyrronium bromide + Indacaterol maleate	Ultibro Breezhaler	Novartis	Drug, Lactose monohydrate, Magnesium stearate	Passive, Capsule, Single dose
	Aclidinium bromide + Formoterol fumarate	Duaklir Genuair	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose
Cystic fibrosis infection	Tobramycin	TOBI Podhaler	Novartis	Drug, 1, 2-distearoyl-sn-glycero-3-phosphocholine, Calcium chloride, Sulfuric acid	Passive, Capsule, Single dose
Influenza	Zanamivir	Relenza Diskhaler	GlaxoSmithKline	Drug, Lactose	Passive, Blister strip, Multi-unit dose
Diabetes	Insulin human	Afrezza	Sanofi Aventis	Drug, Fumaryl diketopiperazine, Polysorbate 80	Passive, Cartridge, Single dose
		Exubera (removed from the market)	Pfizer	Drug, Mannitol, Sodium citrate, Glycine, Sodium hydroxide	Active, Blister, Single dose
Schizophrenia/ Bipolar disorder	Loxapine	Adasuve	Teva	Drug	Passive, Disposable

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Table 3 – The nebulizers in the US & UK markets.

Indications	APIs	Products	Manufacter	Formulation	Device
Asthma and COPD	Albuterol sulfate	AccuNeb	Mylan	Drug, Sodium chloride, Sulfuric acid (Solution)	
	Salbutamol	Salbutamol Inhalation Solution	Focus	Drug, Sodium chloride, Dilute sulfuric acid, Sodium hydroxide solution (Solution)	
	Formoterol fumarate	Perforomist	Mylan	Drug, Sodium chloride, Sodium citrate, Citric acid (Solution)	Pari LC Plus nebulizer (with a facemask or mouthpiece) and Proneb Ultra compressor
	Arformoterol tartrate	Brovana	Sunovion	Drug, Sodium citrate, Citric acid (Solution)	Pari LC Plus nebulizer (with mouthpiece) and Pari Dura Neb™3000 compressor
	Olodaterol	Striverdi Respimat	Boehringer Ingelheim	Drug, Benzalkonium chloride, Edetate disodium, Anhydrous citric acid (Solution)	Spiriva Respimat inhaler
	Tiotropium	Spiriva Respimat	Boehringer Ingelheim	Drug, Edetate disodium, Benzalkonium chloride, Hydrochloric acid (Solution)	Spiriva Respimat inhaler
	Budesonide	Pulmicort Respules	AstraZeneca	Drug, Sodium chloride, Sodium citrate, Citric acid, Disodium edetate, Polysorbate 80 (Suspension)	Pari-LC-Jet Plus Nebulizer/Pari Master compressor system
	Cromolyn sodium	Intal Nebulizer	Sanofi Aventis		
	Tiotropium + Olodaterol	Stiolto Respimat	Boehringer Ingelheim	Drug, Water for injection, Benzalkonium chloride, Edetate disodium, Hydrochloric acid (Solution)	
	Ipratropium bromide + albuterol	Combivent Respimat	Boehringer Ingelheim	Drug, Benzalkonium chloride, Edetate disodium, Hydrochloric acid (Solution)	Combivent Respimat inhaler
	Ipratropium bromide + albuterol sulfate	Duoneb	Mylan	Drug, Sodium chloride, Hydrochloric acid, Edetate disodium (Solution)	Pari LC Plus nebulizer (with face mask or mouthpiece) and Proneb,compressor
Bronchospasm	Albuterol sulfate	Ventolin Solution	GlaxoSmithKline	Drug, Benzalkonium chloride, Sulfuric acid (Solution)	
	Levalbuterol hydrochloride	Xopenex	Sunovion	Drug, Sodium chloride, Sulfuric acid (Solution)	Pari LC Jet and Pari LC Plus nebulizers and PARI Master Dura-Neb 2000 and Dura-Neb 3000 compressors
Cystic fibrosis infection	Tobramycin	Bethkis	Chiesi	Drug, Sodium chloride, Sulfuric acid (Solution)	Pari LC Plus Reusable Nebulizer and Pari Vios Air compressor
		Tobi	Novartis	Drug, Sodium chloride, Sulfuric acid, Sodium hydroxide (Solution)	Pari LC Plus Reusable Nebulizer and DeVilbiss Pulmo-Aide compressor
		Kitabis Pak	Pulmoflow	Drug, Sodium chloride, Sulfuric acid, Sodium hydroxide (Solution)	Pari LC Plus Reusable Nebulizer and DeVilbiss Pulmo-Aide air compressor
	Aztreonam	Cayston	Gilead	Drug, Sodium chloride, Lysine (Solution)	Altera Nebulizer System
	Dornase alfa	Pulmozyme	Genentech	Drug, Sodium chloride, Dornase alfa, Calcium chloride dihydrate (Solution)	eRapid Nebulizer System (eRapid)
Infection	Ribavirin	Virazole	Valeant		I-neb AAD System
Pulmonary arterial hypertension (PAH)	Iloprost	Ventavis	Actelion	Drug, Ethanol, Sodium chloride, Tromethamine, Hydrochloric acid (Solution)	I-neb AAD (Adaptive Aerosol Delivery) System
	Treprostinil	Tyvaso	United Therap	Drug, Sodium chloride, Sodium citrate, Sodium hydroxide, Hydrochloric acid (Solution)	Tyvaso Inhalation System
Nicotine withdrawal symptoms	Nicotine	Nicotrol	Pfizer	Drug, Menthol (Solution)	Nicotrol Inhaler

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fill weight. The container **headspace** is filled by the vapor of propellant; following actuations during the pMDI use, the headspace of canister increases and more propellant evaporates to fill the headspace, which causes the concentration of drug in the liquid phase of the formulation and thus influences the delivered dose content uniformity through container life [24]. The actuator atomizes the formulation, thus its orifice diameter influences the drug particle size distribution. The **orifice** diameter **usually ranges from** 0.14 mm to 0.6 mm [25]. The fine particle dose and fine particle fraction can be increased by utilizing smaller orifice diameter actuators [26]. The effect of the actuator orifice size on the amount of fine particles is more pronounced for solution pMDIs than for suspension ones, as the particle size of the drug substance is the limiting factor of the final particle size of pMDIs.

2.3. *Patient use*

Since the first pMDI was introduced to the market, pMDIs have been evolving throughout the years to be more effective, giving it an important role in inhalation therapy because of the low price, low maintenance and convenience of use. From the point of patient use, pMDIs actively deliver drug aerosols. All pMDIs have the **same drug delivery mechanism.** They use high-pressure liquefied propellants to atomize the formulation into small droplets capable of delivering drug into the deep regions of the respiratory tract [7]. Thus all pMDIs show similar size and shape, and require similar inhalation technique when being used. The **major drawback** for pMDIs is the requirement for coordination between actuation and patient inhalation, and poor coordination may result in high drug deposition in the throat region [27]. This can be overcome by using breath-actuated pMDI device such as Qvar Autohaler, a spacer or a valved holding chamber. Spacers and valved holding chambers increase the delay time between actuation and inhalation, allowing more time for propellant evaporation, and decelerate the particles, and thus they not only help the coordination, but they also increase the pulmonary deposition [28,29]. In 2003, the FDA recommended (but did not mandate) the addition of dose counter or dose indicator on pMDIs to help patients ascertain the remaining dose during use [30]. The dose counter has been observed in many market products, as shown in Table 1.

Clinically, all the current marketed pMDIs are for bronchospasm in asthma and COPD. The pMDI of albuterol, a short acting β_2-agonist (SABA), is still the most widely used medicine for the treatment or prevention of bronchospasm. The pMDI of levabuterol (Xopenex), the R-enantiomer of albuterol, was also launched. It was reported that levabuterol can stereoselectively bind with the β_2-agonist **receptor**, which may enhance the efficacy and reduce the toxicity [31]. As recommended by the Global Initiative for Asthma guidelines, the ideal maintenance treatment for asthma is a combination of long acting β_2-agonists (LABA) and inhaled corticosteroids (ICS). Salmeterol and formoterol are representatives of the LABA family that can reside for an extented period of time at the receptor due to their hydrophobic property, thus providing a long duration of action [32]. Among the five available pMDIs of LABA/ICS combination in the market (Table 1), four products consist of formoterol, possibly due to the fact that formoterol not only has a long acting duration (>12 h), but also a fast onset of action (<3 min) [32]. The pMDI available for COPD therapy is Atrovent, which contains **ipratropium bromide**, a short-acting muscarinic antagonist (SAMA). A combination pMDI containing ipratropium bromide and albuterol (Combivent CFC) is no longer available following the phaseout of CFC pMDIs.

3. DPIs

3.1. *Formulation*

The formulation compositions of DPI can be simple, mostly a blend of micronized drug powder with larger carrier particles (usually lactose monohydrate), or even pure micronized drug powder (such as Pulmicort Turbuhaler). The production of DPI formulation, however, has many particle engineering challenges from drug crystallization and micronization, mixing and blending of micronized drug(s) with carrier excipients, filling of dry powder formulation into capsule/blister/inhaler, storage stability (e.g., aggregation, moisture uptake, etc.), to emptying of powder from the inhaler when being used. Such a formulation process is well reviewed by Telko and Hickey [33]. Most DPI products in the market (Table 2) use a blend of micronized drug (usually <5 μm) and coarse lactose particles (30–80 μm or larger) as carriers. It is important to first characterize the shape and surface morphology of drug substance, because its crystal habit influences its particle aerodynamic behavior, thus further affecting the lung deposition [33]. For example, elongated and pollen-shaped particles have been found to exhibit higher lung deposition efficiency [34,35]. Milling is currently still the mostly widely used method to micronize drug substance. Amorphous drug or excipient could be produced during the milling process, which may lead to reduced flowability and dispersibility of the DPI formulation. Furthermore, once re-crystallization occurs in the formulation, capillary force and solid bridge may be formed due to the release of excess water, thereby impacting the physical stability of mixture [36]. These amorphous materials can be induced into crystals by conditioning them in a humidity controlled or organic solvent vapor environment [37,38]. Another strategy to improve drug dispersibility is to modify the particle surface morphology by producing wrinkled or hollow-porous particles. It has been shown that enhanced aerosol performance of corrugated bovine serum albumin (BSA) powder than smooth spherical BSA powder, which could be explained by the lower contact area caused by the asperities of corrugated particles [39]. The hollow-porous particle as a novel formulation technique has been intensively investigated. Due to characteristics such as lower density and larger size, active ingredients are readily dispersed by means of being contained [40]. The lactose is used as carrier to reduce drug particle aggregation and to improve the formulation flowability. In order to achieve the desired respiratory size (generally <5 μm), the micronized drugs are cohesive and normally form agglomerates due to their small size and high relative surface area [41]. By adding larger lactose particles, the ordered mixture could be formed, in which the fine drug particles will adhere to the surface of lactose particles, thereby leading to good content uniformity and flowability [42]. Fine lactose particles can also be added to promote drug release from the coarse lactose particles, thus enhancing drug dispersibility and fine particle

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fraction [43]. Due to the above reasons, occupation of active sites and co-agglomeration with drug particles as two major mechanisms have been concluded by Jones and Price [44]. Drug dispersibility can also be affected by the morphology of coarse lactose particles, such as the surface roughness and particle shape [45,46]. Some recently developed DPI products, such as Anoro Ellipta and Ultibro Breezhaler, have magnesium stearate except for lactose in the formulations. It was reported that magnesium stearate is hydrophobic, which can provide moisture resistance, thus improving the formulation storage stability [47]. The mechanofusion with magnesium stearate also seems to increase the fine particle fraction (FPF) of DPIs, thereby delivering the drugs more effectively. The increased FPF might be attributed to the appropriate increase of surface energy and the homogenizing of the surface adhesiveness [48]. Mannitol is an alternative to lactose for drugs such as peptides or proteins (e.g., in Exubera insulin DPI), as these drugs may interact with the reducing sugar function of the lactose through Maillard reaction [49]. The formulation–excipients blend homogeneity is not only affected by the physicochemical properties of drugs and excipients, but also by the production factors such as mixer selection and mixing process control [50–52]. Pulmicort Turbuhaler contains a soft spherical pellet formulation of pure drugs without any excipients, which avoids the blend problems [53]. Other drug powder production techniques also include spray drying, freeze drying, solvent precipitation and others [54,55]; for examples, the PulmoSphere and TechnoSphere technologies have been commercialized with the regulatory approval of TOBI Podhaler and Afrezza, respectively. The engineered particles obtained from these technologies not only contribute to the improvement in drug dose consistency and lung target, but also facilitate the transport of active drug across the biological membranes, resulting in a rapid onset of action [56–58].These technologies can be used for drugs with large doses.

3.2. *Device*

There are about 30 marketed DPIs and dozens of new devices that are being reported [5]. All available DPI devices in the US and UK markets are passive inhalers, which rely on patient's breath to activate the drug delivery; therefore it is important that the DPI device is independent of the patient's inspiratory effect [59]. DPI devices can be sorted into single dose inhaler, reservoir based multi-dose inhaler, blister or cartridge based multi-dose inhaler, and single use (disposable) inhaler. For single dose inhaler, the pre-metered formulation is packaged in a hardcapsule (e.g. Spiriva Handihaler), a blister (e.g. Exubera), or a cartridge (e.g. Afrezza). Most marketed DPIs are reservoir based devices (Table 2) in which sufficient formulation is stored in a chamber reservoir and a fixed amount of powder is metered into a dosing receptacle for each dose. The most reknown DPI device is the Advair Diskus, which is a multi-unit device containing a foil blister strip filled with pre-metered formulation. Its next generation device, Ellipta, is the first DPI that enables simultaneous delivery of two drugs without the need for co-formulation. The recently approved Adasuve DPI utilizes a single use device. Such disposable device can be a good option for drugs which only require a single or several doses to complete its course such as vaccine. The details of new types of DPI device have recently been reviewed by Chan et al. [1]. For all these types of DPIs, the usability of the device is important in order to improve the **patient compliance** with the treatment instruction and adherence to the therapy [60]. The factors of the device usability include, but not are limited to, robustness, ease of use, low occurrence of errors, and ergonomics. In contrast to MDIs, each DPI has its own design with a different drug delivery mechanism, thus requiring a different inhalation instruction. Therefore, it is fair to consider "each DPI as one dosage form", mainly based on the different designs of devices. These features could be reflected on the dispersion mechanisms, air flow resistance and flow rate dependence of dry powder delivery devices.

3.3. *Patient use*

In contrast to pMDIs, DPIs deliver the drugs by utilizing the patient's inspiration, thus avoiding the hand and breath coordination for patient use. Such an advantage, however, may also become an issue if the activation of a DPI is flow rate dependent. Take Turbuhaler for example; it has been confirmed that the increase of the air flow through budesonide/formoterolTurbuhaler from 30 to 60 l/min led to approximately double the total emitted dose and fine particle mass of both drugs [61]. For the treatment and prevention of bronchospasm in asthma and COPD, the current DPI products have covered the drug categories of SABA (short-acting β_2 agonist), LABA (long-acting β_2 agonist), SAMA (short-acting muscarinic antagonist), LAMA (long-acting muscarinic antagonist), and ICS (inhaled corticosteroid). Multiple combination DPIs of ICS/LABA are available and new device based combination DPIs are continuously being launched. The recently approved Breo Ellipta is the first member of the ICS/LABA class to shift from twice-daily to once-daily treatment [62,63]. Another category of combination DPIs that consists of LAMA/LABA are formulated for COPD treatment. The utilization of DPIs is being expanded to drugs for new indications, including antibiotics, antivirus, insulin, and vaccines. The DPI of tobramycin (TOBI Podhaler) is introduced to reduce treatment time and improve ease of use compared with tobramycin inhalation solution in cystic fibrosis (CF) patients. It is comparable to inhalation solution in efficacy outcomes and safety profile but has greater patient satisfaction in all the age groups [64]. Although Pfizer's inhaled insulin DPI (Exubera) was withdrawn due to poor reception in the market, its successful launch in 2006 started a new era for inhalation therapy as a route for systemic drug administration. The launch of the second insulin DPI, Afrezza, is an indication of continuous efforts from pharmaceutical industries to apply the DPI technology to systemic drugs.

4. Nebulizers

4.1. *Formulation*

Nebulizers are the oldest device for respiratory drug delivery. The drug is formulated in aqueous solution or suspension, which is atomized into fine droplets via an external nebulization source while being used for inhalation. These aqueous-based oral

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inhalation solutions and suspension must be sterile, and are typically packaged in single-use containers (usually 1–3 ml) [65]. Sterile water for injection is normally used as solvent, and in some cases, ethanol can also be used as the co-solvent. Sodium chloride is usually used to adjust the isotonicity. In most cases, pH values are adjusted by acid or base, such as hydrochloric acid or sodium hydroxide. For easily oxidized drugs, edetate disodium is added in formulation as a chelating agent to further remove the traced metal ions, and nitrogen is used for sparging, filling and pouching. Surfactants such as polysorbate 80 can be used to enhance the suspension stability (such as Pulmicort Respiles). Antimicrobial preservatives such as benzalkonium chloride are added if needed. Inhalation of nebulized solution/suspension requires performance tests of drug delivery rate (output) and aerodynamic droplet size distribution, which are the product's critical quality attributes (CQAs). It is important to study well and understand how the key formulation parameters, such as viscosity, surface tension and drug concentration, influence these CQAs [1,66]. It was reported that an increase of solution viscosity could slow down the nebulization and reduce the drug output for jet nebulizers, and the primary droplet size was proportional to the surface tension [67]. For the vibrating mesh nebulizers, increasing solution viscosity decreased droplet size, but prolonged nebulization time. The electrostatic charges present in the aqueous solutions inhibited the flow and detachment of fluid through the mesh, and the introduction of electrolytes could suppress the charges, thus improving particle size, drug output and nebulization time [68]. The drug concentration influenced the nebulizer output and such an effect was related to the type of nebulizers. When antibiotic concentration was increased, the output decreased more precipitously with the ultrasonic nebulizers than with the jet nebulizers. The drug concentration had less effect on the droplet size distribution [69].

4.2. *Device*

Jet nebulizer, powered by compressed air, is still the most utilized apparatus for inhalation solution/suspension. But the jet nebulizer is cumbersome and somewhat noisy to use, and has a long dosing duration (10–15 minutes). The cooling effect of jet nebulizers due to the expansion of atomizing gas and evaporation of solvent also influences patient's use. Ultrasonic nebulizer generates aerosol by electronically induced vibration of a ceramic piezoelectric element. It is compact and silent, and the dosing time is shorter than that of the jet nebulizers, as the emit of ultrasonic nebulizers is higher than that of jet nebulizers [70]. Heat, however, is generated during the ultrasonic nebulization process, thus it is unsuitable for heat sensitive drugs [71]. Vibrating mesh nebulizers are a recent technology that uses vibrating perforated mesh to generate respirable sized droplets. They are electronic devices and have advantages over both jet and ultrasonic nebulizers, such as fast treatment time, minimal residual dose, and reduced drug waste. Clog of the tiny holes of the mesh and high cost are the drawbacks [72]. A portable nebulizer device, Spiriva Respimat, has been launched by Boehringer Ingelheim. The nebulized solution is filled into a plastic container crimped into an aluminum cylinder (cartridge) for use with the Respimat inhaler. The Respimat inhaler is a handheld, pocket sized oral inhalation device that uses a compressed spring producing mechanical energy to generate a slow-moving aerosol cloud of medication from a metered volume of the drug solution. Due to its difference in terms of atomization mechanisms and device designs, the device is yet to be classified as nebulizer while someone prefers to consider it as propellant free MDI or metered dose liquid inhaler (MDLI) [73]. Such a portable device contains multiple doses and is able to deliver the drug in a single breath of soft mist without the need for continuous inhalations, and thus should be the future direction for new nebulizer development.

4.3. *Patient use*

Currently nebulizers remain widely utilized in hospitals and home settings. They allow the patients to inhale the drug aerosols with tidal breathing maneuvers and little training required. Therefore, it can be used for patients who are unable to coordinate their breathing or activate the inhalers such as MDI or DPI, especially for the elderly and children. Most inhalation solutions/suspensions for asthma and COPD consist of one active drug of SABA, LABA or LAMA. Most recently, the FDA approved the inhalation spray of LAMA/LABA (Tiotropium/Olodaterol) combination, which can be given to patients once daily.

Nebulizers can continuously deliver drugs for a long dosing duration, thus are suitable for large dose drugs, such as antibiotics. Tobramycin was the first antibiotics approved as an inhalation solution (TOBI) for the prevention and treatment of *Pseudomonas aeruginosa* infection in cystic fibrosis. A long-term therapy study indicated that inhaled tobramycin improved lung function and reduced exacerbation rate for patients with CF [74]. The other clinical applications of nebulizers include pulmonary arterial hypertension and nicotine withdrawal symptoms (Table 3).

Nebulizers are not typically used for chronic-disease management because they are larger and less convenient than pMDIs and DPIs. It is critical that the inhalation solution/suspension should be delivered using the specific nebulizer recommended in drug package insert in order to obtain the expected emitted dose, particle size distribution and formulation emptying time while being used [75]. Different droplet size distribution was observed with the same nebulizer while **different compressors** or different compressor pressures were utilized [69]. With traditional jet nebulizers, only 10% of the dose may reach the lung. The majority of the drug is either remaining in the nebulizer or released into the surrounding air during expiration [67]. Breath enhanced device (e.g. Pari LC Star) or breath actuated device (e.g. AeroEclipse II) have been developed to create aerosols only during inspiration, thus reducing drug wastage and improvimg delivery efficiency [66,76].

5. Regulations on development of inhalation drug products

The FDA and EMA have published guidelines on the development of all these three types of inhalation drug products (pMDI, DPI and inhalation solution/suspension for nebulizer) [7,65,77]. Following the patent expiration for many inhalation products, especially the blockbuster drugs such as Advair Diskus,

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the switch from branded to generic inhalation medicine is a worldwide trend, and the development of generic inhalers has been a hot area for pharmaceutical industries.

The EMA in 2009 issued the guideline on the demonstration of therapeutic equivalence between two inhaled products, which described a step-wise approach for the approval of generic inhalation drug products [78]. From the point of formulation, the generic and the reference products should be the identical dosage form with the same active substance(s). Any differences in crystalline structure and/or polymorphic form of the active substance and any qualitative and/or quantitative differences in excipients should not influence the pharmaceutical performance and safety profile of the product. Regarding the device, the handling and resistance to airflow of the generic and reference products should be the same. The critical quality attributes to assess the *in vitro* equivalence between the generic and reference products are the dose delivery uniformity and particle size distribution profile. The delivered dose should be similar (within 15%). The comparison of particle size distribution, tested by a validated multistage impactor, should be performed per impactor stage or justified group of stages with suitable equivalence criteria (e.g. 15% may be justifiable). If a generic product satisfies all of the above pharmaceutical criteria for equivalence, the use of only *in vitro* data may be considered acceptable for product approval. Otherwise, *in vivo* studies (pharmacokinetics or pharmacodynamics) should be performed to substantiate equivalence.

Rather than issuing a general guideline as the EMA did, the FDA has published five separate draft guidance for each specific inhalation product: pMDIs of albuterol sulfate, ipratropium bromide, levalbuterol tartrate, budesonide/formoterol fumarate, and DPI of fluticasone propionate/salmeterol [79–83], starting from 2013. Based on the FDA guidance, it will be a very difficult process to get FDA approval in the US for generic product as it requires that the *in vitro* tests, pharmacokinetics and pharmacodynamics all substantiate equivalence [84]. The *in vitro* tests include single actuation content (SAC) and aerodynamic particle size distribution (APSD). Equivalence in spray pattern, plume geometry, priming and repriming studies are also required for generic pMDIs, apparently for supporting the similarity of valves and actuators. The similarity requirements of DPI device include the device mechanism, pre-metered multi-dose format, doses, operating procedures, size, shape, device resistance and dose counter. For the formulation, the generic product should use the same inactive ingredient(s) as the reference product (i.e. qualitative sameness; Q_1), and the concentration of the inactive ingredient(s) used in the generic product should be within 5% of those used in the reference product (i.e. quantitative sameness; Q_2). The draft guidance has been challenged by industries. Rather than the Q_2 requirement, it is proposed to utilize the quality-by-design (QbD) approach to study the control space of the excipient concentration for the generic product [85].

6. Conclusions

pMDI, DPI and nebulizer each has its specific advantages and limits. The increasing interest in the pulmonary route for both local and systemic acting drugs continues to promote the development of new inhalation drug products for new indications, together with new formulation and device technologies. The development of inhalation drugs should practically consider factors such as patient preference, convenience of use, and cost, as the final target goal is to improve patient adherence and therapeutic outcomes.

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