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REVIEW

Dry powder inhaler for pulmonary drug delivery: human respiratory system, approved products and therapeutic equivalence guideline

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Abstract Pulmonary drug delivery is the promising delivery route to treat not only respiratory diseases but also systemic diseases and has proven as a potential delivery route for complex drugs that cannot be delivered orally. Development of dry powder inhalation systems targets the delivery of fine drug particles to the deep lung surface by a combination of particle deposition and clearance in human respiratory tract. Various dry powder inhalers (DPIs) with their advanced technologies have been proposed and marketed to treat pulmonary diseases such as asthma, chronic obstructive pulmonary diseases, cystic fibrosis and furthermore, systemic diseases such as diabetes and schizophrenia. Bioequivalent therapeutic effects can be derived from generic products that provide additional benefits to the patients and the health care system. Currently, European Medicines Agency (EMA) have established the bioequivalent methods to develop and approve the inhaled products. This review covers the anatomical and physiological characteristics of human respiratory tract to understand the mechanism of drug deposition and clearance. Also, therapeutic areas for both local and systemic treatment, DPI products and their advanced technologies are presented. Finally, European Medicines Agency (EMA) guidelines for inhaled products are presented to demonstrate the therapeutic bioequivalence between generic and reference products.

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Introduction

The lungs are an attractive route for drug delivery, as they have high-solute permeability, a large surface area for absorption, and limited proteolytic activity (Patton 1996). Pulmonary drug delivery allows for a non-invasive delivery of biotherapeutics, compared to parenteral invasive delivery. For instance, pulmonary drug delivery allows for the administration of peptides and proteins, which cannot be orally delivered because of enzymatic degradation and poor intestinal membrane permeability (Hamman et al. 2005).

Both industry and academia have taken interest in pulmonary drug delivery, as it has a great variety of applications and advantages for use in the pharmaceutical field. For instance, inhalation therapy is now widely accepted for localized treatment for pulmonary diseases, such as asthma and chronic obstructive pulmonary disease (COPD) (Chan et al. 2014). Pulmonary drug delivery also serves an alternative route for systemic drug administration for diseases, such as diabetes (Chan et al. 2014). Moreover, pulmonary drug delivery can avoid first-pass metabolism, reducing the overall dose and amount of side effects that result from high levels of systemic drug exposure (Sung et al. 2007). For local activities, orally-inhaled drugs are delivered directly to the site of action in the lung, providing fast onset of action (within five minutes) (Lavorini et al. 2014). Utilizing long-acting drugs (e.g., salmeterol and tiotropium) and/or modifying formulation technology can achieve sustained activity and better meet clinical needs and patient compliance (Beck-Broichsitter et al. 2012).

Modern inhalation drug products are commonly classified into three categories: (1) pressurized metered dose inhaler (pMDI); (2) nebulizer; (3) and dry powder inhaler (DPI). pMDIs are either suspension or solution based formulation of drug in propellants. For many years, the pMDI has been the leading category for the application of inhalation therapy. It has favourable features, such as easy handling, high reliability, and accurate metering performance. The traditional chlorofluorocarbon (CFC) propellants, which have previously been used in pMDI for decades, were banned by the Montreal Protocol (1989) due to their ozone depletion effect and hydrofluoroalkanes (HFA) were selected as alternative propellants. However, traditional pMDIs also have a number of important drawbacks. For example, they require the coordination between actuation and patient inhalation and the poor coordination may result in high drug deposition in the throat region. This phenomenon occurs in the HFA-pMDI which is used instead of CFC-pMDI (Dalby et al. 2004). Nebulizers convert a liquid solution or suspend a drug into fine droplets by air-jet or ultrasonic means. Nebulizers are thus very efficient at creating mists of extremely fine droplets with good pulmonary deposition. Nebulized treatment may be considered a good choice for patients who need very high drug dose such as antibiotic therapy (Boe et al. 2001). However, a patient can take several minutes to inhale a dose from a nebulizer. Additionally, these devices have limited portability, considerable size, and operational complexity; therefore, they are primarily used in institutional environments (Malcolmson and Embleton 1998). DPIs represent a significant advance in pulmonary delivery technology. For example, DPIs are breath-actuated. Patients can thus overcome coordination problems, such as synchronizing dose discharge with inhalation and in order to do this, patients must be able to generate a sufficient inspiratory flow in order to release the powder and de-aggregate the drug to generate respirable particles. (Broeders et al. 2001; Atkins 2005). Also, DPIs are potentially suitable for delivering a wider range of drugs, including biopharmaceutical systemic therapies, such as peptides and proteins (Onoue et al. 2008).

This review discusses the anatomical and physiological characteristics of the human respiratory tract to understand the mechanism of drug deposition and clearance. This review also presents therapeutic areas for both local and systemic treatment, as well as approved DPI products and their advanced technologies. Lastly, this review provides a guidelines issued by the European Medicines Agency (EMA) for inhaled products to demonstrate the therapeutic bioequivalence between generic products and reference products.

Respiratory system

The respiratory tract is the organ of gas exchange. It has the nickname "the organ of life" due to its vital role in the human body (Island 1916). Specifically, the physiological roles of the respiratory system are: (1) to deliver oxygen; (2) to remove carbon dioxide; endogenous wastes and toxins; and (3) to defend against outside intruders (Cotes et al. 2009; Mansour et al. 2013). The human respiratory tract can be divided into three anatomical regions including extra-thoracic, thoracic, and pulmonary region. The extra-thoracic region includes the nose, nasal cavity, pharynx, laryngeal region. The thoracic region includes tracheobronchial tree including trachea and bronchus. The pulmonary region consists of alveolar ducts and alveolar sacs where gas exchange takes place (Fig. 1) (Verma et al. 2015). Breathing is normally possible through either the nose or the mouth, and the two alternative air passages converge in the oropharynx. Nasal breathing is the normal way of breathing, and has two major advantages over mouth breathing: (1) filtration of particulate matter by the nose hairs; and (2) better humidification of inspired gas (Cooper et al. 2009). However, the nose may offer more resistance to airflow than the mouth, and nasal resistance may make oral breathing obligatory (Lumb 2016). Larynx has many physiological roles: (1) regulating the respiratory route and airflow; (2) exerting a circulatory function in promoting venous return; (3) acting as a sphincter in fixation of the throat during cough and expectoration, and for protective closure during swallowing and vomiting; and (4) allowing for phonation and speech (Pressman and Kelemen 1955; Clarke 2015).

Following the inhalation therapy of DPIs, only a fraction of the dose reaches the expected target area. Knowledge of the amount of drug actually deposited is essential in designing the delivery system or devices to optimize the delivery efficiency to the targeted region of respiratory tract. This knowledge is essential in developing DPIs, such as a dosing regimen to deliver the required amount of active compound to the patient. Airway geometry of human respiratory tract and mechanism of deposition and clearance are several factors that affect the deposition pattern of DPIs and thus, it is important to understand these factors. For this purpose, in this chapter, anatomy and physiology of human respiratory tract are concerned and deposition and clearance mechanism have been studied.

Anatomy and physiology of human lung bronchial tree

The airways can be divided into two distinct, functional zones: (1) conducting zone and (2) respiratory zone (Høiby et al. 2010). There is no consensus on how to describe these zones, as an accurate and complete model of the branching pattern of the human bronchial tree

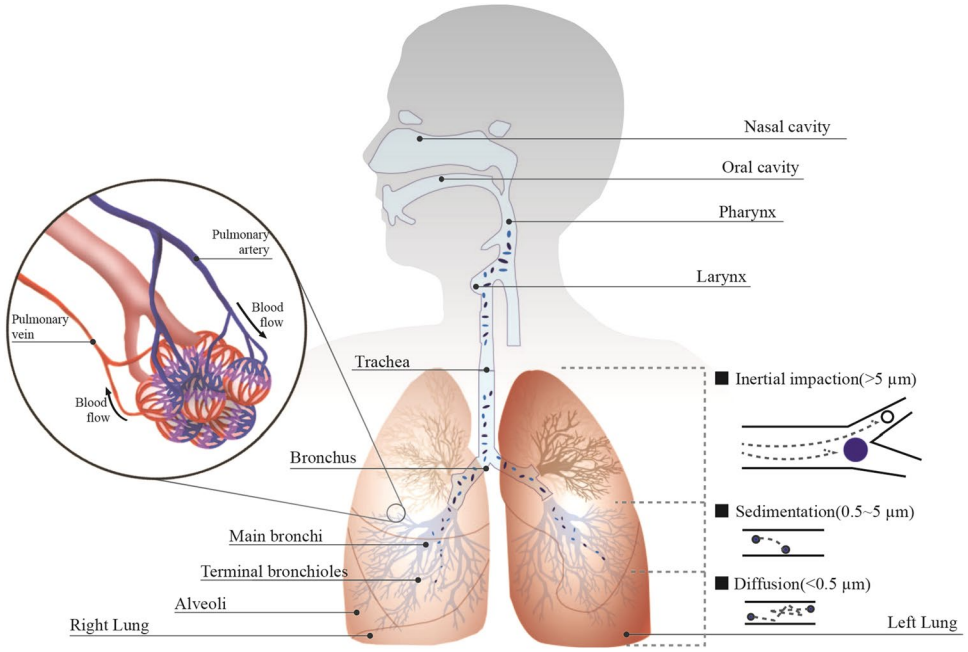

Fig. 1 A schematic diagram of the human respiratory tract and mechanism of particle deposition

remains elusive. Several mathematical models have been proposed. The most useful and widely-accepted approach remains that of Weibel (Weibel 2001). It divided the lungs into 24 compartments, and numbers successive generations of air passages from the trachea (generation 0) down to the alveolar sacs (generation 23). This model assumes that each bronchus regularly divides into approximately two equally-sized bronchi. The conducting zone includes generations 0 (trachea) to 16 (terminal bronchioles); the respiratory zone includes generations 17 to 23, which include the respiratory bronchioles, the alveolar ducts, and the alveolar sacs (Clarke 2015; Verma et al. 2015; Lumb 2016). Table 1 shows the characteristics of generations of airways in the tracheobronchial tree. The airway diameter reduces with each division from trachea (generation 0) to bronchioles (generation 16). As the number of generation increases, the cross-sectional area increases and the gas velocity decreases. The respiratory zone is also called the acinar airways where gas exchange occurs (Hastedt et al. 2016).

Table 1 Structural characteristics of airways in tracheobronchial tree

	Generation		d (cm)	l (cm)	Number	Cross-section area (cm^2)	Cartilage	Epithelial cell type
Conducting zone	Trachea	0	1.8	12.0	1	2.54	Open rings	Columnar ciliated
	Bronchi	1	1.22	4.8	2	2.33		
		2	0.83	1.9	4	2.13	Plates	
		3	0.56	0.8	8	2.00		
	Bronchioles	4	0.45	1.3	16	2.48		
	Terminal bronchioles	5	0.35	1.07	32	3.11		
		↓	↓	↓	↓	↓		
		16	0.06	0.17	6×10^4	180.0	Absent	Cuboidal
Respiratory zone	Respiratory bronchioles	17	↓	↓	↓	↓		Cuboidal to alveolar
		18						
		19	0.05	0.10	5×105	10^3		
	Alveolar ducts	20	↓	↓	↓	↓		Alveolar
		21						
		22						
	Alveolar sacs	23	0.03	0.03	8×10^6	10^4		

Aerosol deposition and clearance mechanisms in the lung

Many factors influence the phenomenon of aerosol deposition of inhaled particles in different regions of the respiratory system. These factors include particle size, particle shape, breathing rate, lung volume, respiration volume, and health condition of the individual (Taulbee and Yu 1975). Particles administered by the pulmonary route are generally categorized, based on their size, into large particles (≥ 5 μm), fine particles (0.1–5 μm), and ultrafine particles (≤ 0.1 μm) (Heyder et al. 1986). Particle deposition occurs by three main mechanisms: impaction, sedimentation, and diffusion (Fig. 1) (Bell 1974). Impaction is the primary mechanism for particle deposition, in particular for large particles of aerodynamic diameter ≥ 5 μm. Impaction is a flow-dependent mechanism. Large particles (≥ 5 μm) with high velocity do not follow the flow of the air stream, due to inertia causing the particles to impact the wall of airways and consequently deposit there. This mechanism is common in the upper airways of the lung (trachea–bronchial region), where air velocity is high and the airflow is turbulent (Carvalho et al. 2011). Sedimentation is a secondary deposition mechanism. It occurs in the low-airflow regions, such as the lower bronchial airways and alveolar region (Tena and Clarà 2012). Gravitational force governs the sedimentation of particles. Sedimentation increases with an increase in particle size and a decrease in flow rate. Particles in the range of 0.5–5 μm may avoid impaction in the upper airways but then deposit by sedimentation in the lower tracheobronchial and alveolar regions (Cheng 2014). Diffusion is the last deposition mechanism for particles less than 0.5 μm and is caused by Brownian motion. Diffusion increases with decreasing particle size and airflow rate, and thus becomes an important mechanism for particle deposition in the lower airways and alveolar region. Particles move from high-to-low concentrations across airflows, and deposit upon contact with the airway wall (Verma et al. 2015; Wright 2016).

After inhalation of aerosol particles, blood or the lymphatic system absorbs the particles, or they degrade by drug metabolism and get cleared from the lung. With the latter option, the respiratory system uses various clearance mechanisms in different regions of the system (Verma et al. 2015). For instance, mucociliary clearance provides an important defense mechanism for removing insoluble inhaled particles, which is prevalent in the upper airways (Lee et al. 2013). The mucociliary clearance acts as a potential physical barrier for drug penetration. Within 24 h, this mechanism clears the majority of deposited particles in the trachea-bronchial region. The clearance mechanism of the respiratory system also includes mechanical clearance, which means coughing, sneezing, or swallowing of inhaled particles in the upper airway. This mechanism occurs unconsciously and instantly after inhaling large particles (Hastedt et al. 2016). Enzymatic degradation is the main clearance mechanism in lungs. Although the amount is small compared to the liver, lungs have several degradation enzymes. These include: (a) CYP450 enzymes in lung epithelia; (b) lung-specific CYP2S and CYP2F, which are isomers of CYP450; (c) phase 2 metabolic enzymes, such as esterase and peptidases (Verma et al. 2015). The final mechanism is alveolar macrophages. These are the dominant phagocytic cells in the lungs. Alveolar macrophages account for up to 90% of the leukocytes in airspace. They reside in the alveolar lumen and clear inhaled particulates, remove dying cells, and maintain alveolar homeostasis (Janssen et al. 2016).

DPI approved products with therapeutic classification

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Successful delivery of drugs into the deep lungs depends on the integration between powder formulations and the device performance. In this chapter, therapeutic area is divided into localized treatment including asthma, COPD, cystic fibrosis, tuberculosis and systemic treatment including diabetes and schizophrenia. Marketed products for each disease and its characteristics, formulations and device types are presented in Table 2 and important, innovative products are described in detail in following chapter. For local activities, the orally inhaled drugs are delivered directly to the site of action in the lung, providing fast onset of action and sustained activity can also be achieved by using of long-acting drugs and by modifying formulation technology. 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 and also provides avoiding first-pass metabolism and thus show an improved bioavailability.

Asthma and chronic obstructive pulmonary disease (COPD)

Asthma and chronic obstructive pulmonary disease (COPD) are major worldwide diseases. Experts estimate COPD will be the third-highest cause of death by 2030 (Vestbo et al. 2013). The primary risk factor of COPD is tobacco smoke, including second-hand exposure. Other risk factors are exposure to biomass fuel smoke and other air pollutants, which may induce a chronic inflammatory response and oxidative stress (Salvi 2014; Lee et al. 2015; Tan et al. 2015). COPD is an inflammatory airway disease that particularly affects the small airways and is highly prevalent

Table 2 Approved DPI products and its characteristics according to therapeutic classification in US and EU

Indication	APIs	Products	Manufacturer	Formulation	Device type	Market
Asthma and COPD	Albuterol sulfate	Proair Respiclick	Teva	Drug Lactose monohydrate	Passive, Reservoir, Multiple dose	US
	Salbutamol sulfate	Pulvinal Salbutamol	Chiesi	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose	EU
		Easyhaler Salbutamol sulfate	Orion	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose	EU
	Terbutaline sulfate	Bricanyl Turbohaler	AstraZeneca	Drug	Passive, Reservoir, Multiple dose	EU
	Salmeterol xinafoate	Serevent Diskus	GlaxoSmithKline	Drug, Lactose monohydrate	Passive, Blister strip, Multiple dose	US
	Formoterol fumarate	Foradil Aerolizer	Novartis	Drug, Lactose	Passive, Capsule, Single dose	US
		Foradil Certihaler	Novartis	Drug, Lactose monohydrate, Magnesium stearate	Passive, Reservoir, Multiple dose	US
		Oxis Turbohaler	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose	EU
		Easyhaler Formoterol	Orion	Drug, Lactose monohydrate	Passive, Reservoir, Multiple dose	EU
	Indacaterol maleate	Arcapta Neohaler	Novartis	Drug, Lactose monohydrate	Passive, Capsule, Single dose	US
		Onbrez Breezhaler	Novartis	Drug, Lactose monohydrate	Passive, Capsule, Single dose	EU
	Tiotropium bromide	Spiriva Handihaler	Boehringer Ingelheim	Drug, Lactose monohydrate	Passive, Capsule, Single dose	US, EU
	Aclidinium bromide	Tudorza Pressair	Forest	Drug, Lactose monohydrate	Passive, Reservoir Multiple dose	US
		Eklira Genuair	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir Multiple dose	EU
	Glycopyrrolate	Seebri Breezhaler	Novartis	Drug, Lactose monohydrate Magnesium stearate	Passive, Capsule Single dose	US
	Umeclidinium	Incruse Ellipta	GlaxoSmithKline	Drug, Lactose monohydrate Magnesium stearate	Passive, Blister strip Multi-unit dose	US
	Budesonide	Easyhaler Budesonide	Orion	Drug, Lactose monohydrate	Passive, Reservoir Multiple dose	EU
		Pulmicort Flexhaler	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir Multiple dose	US
		Pulmicort Turbuhaler	AstraZeneca	Drug	Passive, Reservoir Multiple dose	US
	Mometasone furoate	Asmanex Twisthaler	Merck	Drug, Lactose Anhydrate	Passive, Reservoir Multiple dose	US
	Beclomethasone dipropionate	Pulvinal Beclometasone Dipropionate	Chiesi	Drug, Lactose monohydrate Magnesium stearate	Passive, Reservoir Multiple dose	EU
	Fluticasone propionate	Flovent Diskus	GlaxoSmithKline	Drug, Lactose monohydrate	Passive, Blister strip Multi-unit dose	US
	Fluticasone furoate	Arnuity Ellipta	GlaxoSmithKline	Drug, Lactose monohydrate	Passive, Blister strip Multi-unit dose	US
	Beclomethasone dipropionate + Formoterol	Foster Nexthaler	Chiesi	Drug, Lactose monohydrate Magnesium stearate	Passive, Reservoir Multiple dose	EU

Table 2 (continued)

Indication	APIs	Products	Manufacturer	Formulation	Device type	Market
	Budesonide + Formoterol fumarate	Symbicort Turbohaler	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir Multiple dose	US
		DuoResp Spiromax	Teva	Drug, Lactose monohydrate	Passive, Reservoir Multiple dose	EU
	Fluticasone furoate + Vilanterol	Breo Ellipta	GlaxoSmithKline	Drug, Lactose monohydrate Magnesium stearate	Passive, Blister strip Multi-unit dose	US
	Fluticasone propionate + Salmeterol	Advair Diskus	GlaxoSmithKline	Drug, Lactose monohydrate	Passive, Blister strip Multi-unit dose	US
	Umeclidinium + Vilanterol	Anoro Ellipta	GlaxoSmithKline	Drug, Lactose monohydrate Magnesium stearate	Passive, Blister strip Multi-unit dose	US
	Glycopyrronium bromide + Indacaterol maleate	Ultibro Breezhaler	Novartis	Drug, Lactose monohydrate, Magnesium stearate	Passive, Capsule Single dose	EU
	Aclidinium bromide + Formoterol fumarate	Duaklir Genuair	AstraZeneca	Drug, Lactose monohydrate	Passive, Reservoir Multiple dose	EU
Lung infection/ Cystic fibrosis infection	Tobramycin	TOBI Podhaler	Novartis	Drug, 1, 2-distearoyl-snglycero-3-phosphocholine Calcium chloride, Sulfuric acid	Passive, Capsule Single dose	US
	Colistimethate	Colobreathe	Forest Laboratories	Drug (Encapsulated DPI formulation)	Hand-held inhaler, Turbospin	EU
Cystic fibrosis	Mannitol	Bronchitol	Pharmaxis pharmaceuticals	Drug	Passive, Capsule, Multi dose	EU
Influenza	Zanamivir	Relenza Diskhaler	GlaxoSmithKline	Drug, Lactose	Passive, Blister strip Multi-unit dose	US
Diabetes	Insulin human	Afrezza	Sanofi Aventis	Drug, Fumaryl diketopiperazine Polysorbate 80	Passive, Cartridge Single dose	US
Schizophrenia/ Bipolar disorder	Loxapine	Adasuve	Teva	Drug	Passive, Diposable	US

in older people (Postma and Rabe 2015). Asthma is also a chronic inflammatory disease that affects the large and small airways. Asthma often develops in childhood. The strongest risk factors for developing asthma are a combination of genetic predisposition with environmental exposure to inhaled substances and particles. The inhalation may provoke allergic reactions or irritate the airways with allergens and air pollution (Beasley et al. 2015). Despite both COPD and asthma being inflammatory airway diseases, there are some differences. For instance, asthma generally manifests as an intermittent and reversible airway obstruction, whereas COPD is progressive and irreversible (Sciurba 2004). Asthma and COPD also have major differences in their structural and inflammatory signatures. Asthma includes an elevated IgE, induction of Th2 cells, eosinophilic infiltration, reticular basement membrane thickening and smooth muscle hyperplasia. COPD includes increased neutrophils, induction of Th1, TGBβ-induced small airway fibrosis, goblet cell hyperplasia, and MMP elastic tissue destruction (Fabbri et al. 2003). For the above reasons, topically-inhaled bronchodilators and corticosteroids are the mainstay treatments for asthma and COPD. For instance, to treat bronchoconstriction and inflammation of airways, asthma and COPD treatment guidelines recommend using a combination of long-acting β_2-agonists (LABA) and inhaled corticosteroids (ICS). Superior control of asthma and COPD by ICS/LABA combination therapy has been demonstrated. However, clinical studies suggest that additive and synergic effects result from combination therapy.

There are two ICS/LABA combination products available for maintenance and reliever therapy: budesonide/formoterol (Symbicort®) and salmeterol/fluticasone (Seretide®)

(Miller-Larsson and Selroos 2006). Symbicort® is a widely prescribed asthma product containing both budesonide as ICS and formoterol as LABA in a single inhaler device, Turbuhaler® (Kuna and Kuprys 2002). Turbuhaler® is a passive inhaler device that relies on a patient's breath to activate drug delivery. Turbuhaler® is also a reservoir-based, multi-dose device. It stores a sufficient formulation in a chamber reservoir and meters a fixed amount of powder into a dosing receptacle for each dose (Table 2) (Chan et al. 2014). Seretide® is a combination formulation of fluticasone as ICS and salmeterol as LABA. Seretide® is intended for maintenance therapy of obstructive airway diseases. It uses a single inhaler device, Diskus®. Like Turbuhaler®, Diskus® is also a passive, multi-dose inhaler device with a pre-metered formulation that comes blister packaged (Chapman 2002).

Whereas the use of Diskus® DPI is well established for the delivery of a twice-daily, fixed combination of ICS/LABA, Ellipta® DPI is a once-daily medication and multi-dose inhaler that has been approved by the U.S. Food & Drug Authority (FDA). Breo® Ellipta® combines fluticasone as ICS and vilanterol as LABA. Anoro® Ellipta® combines the long-acting anticholinergic/long-acting beta-2 receptor agonist umeclidinium/vilanterol. Incurse® Ellipta® consists of long-acting anticholinergic umeclidinium monotherapy (Table 2) (Yun Kirby et al. 2016). The Ellipta® DPI has been designed to contain two separate blister strips from which inhalation powder can be delivered. The strips are simple to use with a large, easy-to-read dose counter (Svedsater et al. 2013). The single-strip configuration can deliver the monotherapies. In the two-strip configuration, one dose from each strip can be aerosolized simultaneously to deliver combination therapies. This enables the individual development of product formulations, since they are stored separately until the point of administration (Grant et al. 2015).

Recently, Foster® Nexthaler® is developed with fixed dose drug combination of beclometasone dipropionate as ICS and formoterol fumarate as LABA, with innovative dry powder inhaler that emits extrafine particles (Table 2). Extrafine refers the small particles with MMAD < 2 μm which provides high lung deposition and enables drug particles to reach both large and small airways, thus optimizing treatment of the underlying inflammatory and remodeling process that takes place throughout the entire respiratory tree in asthma and COPD patients. Nexthaler® is the first formulated device to deliver extrafine particles in DPI system. Nexthaler® DPI is a multidose DPI with breath-actuated mechanism (BAM) guaranteeing that the dose is released only when a threshold inspiratory flow of 35 L/min is achieved and this refers a release of consistent full therapeutic dose independently of the flow rate achieved by the patient (Buttini et al. 2016). In addition, Nexthaler® DPI incorporates a feedback system for the patients to provide them the reassurance that a dose has been inhaled. For example, a click is heard on activation of the BAM when the patient inhales through the device and internal dose release mechanism is activated and a dose counter linked to the BAM does not decrement after preparation of the dose but does decrement only after delivery of the full therapeutic dose (Corradi et al. 2014).

Cystic fibrosis

Cystic fibrosis is the most commonly inherited disease, affecting between 1 in 2000 [adults/people] and 1 in 4500+ children of Caucasian origin (Koch and Hoiby 1993). Cystic fibrosis is an autosomal recessive genetic disorder affecting a number of organs. These organs include the lung airways, pancreas and sweat glands. Cystic fibrosis is caused by a dysfunction of the cystic fibrosis transmembrane regulator's (CFTR) epithelial chloride channel (Rommens et al. 1989; Boucher 2002). The malfunctioning of a CFTR protein results in abnormal chloride conductance on the apical membrane of the epithelial cell. In turn, this causes airway surface liquid (ASL) depletion, ciliary collapse, and decreased mucociliary clearance and finally muscus obstruction, infection, and inflammation occur (Ratjen 2009). The ASL is thin layer of fluid covering the luminal (apical) surface of the airway epithelium and plays a key role in airway system. The ASL maintains homeostasis of: pH; ionic and nutrient content; volume for regulating antimicrobial activity; ciliary function; and mucociliary clearance (Boucher 2004). However, in cystic fibrosis, the ASL's ability to maintain homeostasis is impaired, leading to a dehydrated and acidic ASL. This creates a disordered airway milieu and thick mucopurulent secretions. Chronic bacterial infection results, giving rise to chronic airway infections, inflammation, airway damage, and respiratory failure (Haq et al. 2015). Improvement of airway hydration and mucus clearance from the lung is a major therapeutic goal, with the aims of maintaining and/or restoring respiratory function (Zemanick et al. 2010, Mogayzel Jr et al. 2013).

For treatment, mannitol is a sugar alcohol used in medicine as an osmotic agent. When inhaled, it creates an osmotic gradient that facilitates movement of water into the lumen of the airways, thereby increasing the volume of airway surface liquid and improving clearance of mucus (Robinson et al. 1999). Bronchitol® is licensed for the treatment of certain patients with cystic fibrosis to help them clear mucus from their lungs (Nolan et al. 2016). Bronchitol contains the active ingredient mannitol with hyperosmotic properties which developed by spray drying process that changes the naturally irregular structure to precision engineered, 3 micron diameter spheres which enables possible to inhale using a simple inhaler (Glover et al. 2008). Clinical trials have shown that Bronchitol® works by rehydrating the airway/lung surface and promoting productive cough which

helps to increase mucus clearance, and improve the lung function. The recommended dose of Bronchitol® is 400 mg twice a day which requires the inhalation of ten capsules (40 mg per one capsule) via the inhaler device (Table 2) (George et al. 2009).

Inhaled colistimethate sodium is effective for treating pseudomonas aeruginosa. Colobreathe® dry powder for inhalation uses a new encapsulated dry-powder formulation of micronized colistimethate sodium. It is administered via a convenient hand-held inhaler, Turbospin® (Schuster et al. 2012). Antibiotic tobramycin is also an important tool in managing cystic fibrosis and chronic pseudomonas aeruginosa lung infections (Newhouse et al. 2003). Recently, a tobramycin inhalation powder formulation with a portable delivery system, the TOBI® Podhaler®, has been developed (Table 2). Traditional DPI technologies have not been suitable for the delivery of tobramycin to the lung because of the remarkably low drug-dosing amount (VanDevanter and Geller 2011). PulmoSpheres® technology has been developed and produced by an emulsion-based, spray-drying process that yields light porous tobramycin particles with improved flow and dispersion properties and more uniform particle size distributions, when compared with traditionally-milled powders (Geller et al. 2011).

Tuberculosis

Tuberculosis is an infection disease that is a major public health threat and causes death worldwide. Tuberculosis is a poverty-related disease, which disproportionately affects poor, vulnerable, and marginalized population groups wherever it occurs (Sulis et al. 2014). The most frequent symptoms of Tuberculosis are cough, low-grade fever, anorexia, fatigue, night sweats, and weight loss. These symptoms may persist for weeks to months, as a systemic manifestation of Tuberculosis (Leung 1999). *Mycobacterium tuberculosis* spreads by small airborne droplets, called droplet nuclei. They generate when an infected person coughs, sneezes, or talks. These droplets can remain airborne for minutes to hours after expectoration (Knechel 2009). The tubercle bacilli establish infection in the lungs after they are carried in droplets small enough (5–10 μm) to reach another person's alveolar spaces. If the defense system of the new host fails to eliminate the infection, the bacilli proliferate inside alveolar macrophages and eventually kill the cells. Inhalation of *Mycobacterium tuberculosis* leads to one of four possible outcomes: (1) immediate clearance of the organism; (2) latent infection; (3) the onset of active disease (primary disease); (4) active disease many years later (reactivation disease) (Wania 2013).

Tuberculosis is a disease caused by bacterial infection of the lungs like cystic fibrosis, there is wide range of antibiotics administered by orally, however, there is no DPI product. Currently, there have been many DPI studies to treat tuberculosis effectively. Chan HK reported a combination dry powder aerosol containing three, first-line, anti-tubercular drugs. They consist of pyrazinamide, rifampicin, and isoniazid, which can treat drug-susceptible Tuberculosis (Chan et al. 2013). Capreomycin has been formulated as a dry powder. It is applied by spray drying and by using l-leucine as the main excipient. One study found it possible to obtain inhalable particles with a drug content of about 60–93% (Fiegel et al. 2008). Researchers recently conducted a phase I pharmacokinetic study on an inhalable dry powder form of capreomycin, an antibiotic typically administered by injection to treat drug-resistant Tuberculosis (Dharmadhikari et al. 2013).

Systemic diseases (diabetes, schizophrenia)

Inhalation therapy has been widely accepted for localized treatment of pulmonary diseases, such as asthma and COPD. Inhalation therapy is also an alternative route for systemic drug administration for diseases like diabetes and Central nervous system (CNS) disorders. In 2006, the US FDA approved the first formulation of inhaled insulin Exubera® (Pfizer, New York, NY, USA). It is a mealtime, non-invasive alternative to subcutaneous insulin for adults with diabetes (Ceglia et al. 2006). Although inhaled insulin was greeted with enthusiasm, its administration was complex. The US FDA raised concerns regarding lung toxicity, which ultimately resulted in the manufacturer withdrawing Exubera® from the market 1 year after its launch.

In 2014, the US FDA approved a new formulation of inhaled insulin, Afrezza® (Table 2) (Afrezza, Valencia, CA, USA). It is a mealtime insulin for non-smoking adults with diabetes without pulmonary disease (Pittas et al. 2015). Afrezza® is the only ultra-rapid-acting insulin on the market. This insulin has faster pharmacokinetics and pharmacodynamics than the other three, rapid-acting, insulin analogs on the market which are insulin aspart, insulin glusine, and insulin lispro. Afrezza® is a drug-device combination product consisting of a Technosphere™ insulin powder delivered from a small and portable inhaler to help patients achieve blood-sugar control (Klonoff 2014). Technosphere™, developed by Mannkind biopharmaceuticals, is a general drug carrier technology that captures and stabilizes peptides or proteins in small, precipitated particles (Steiner et al. 2002). A well-characterized, small organic molecule, Fumaryl diketopiperazine, self-assembles by hydrogen binding in a mild acid environment into microspheres with a mean diameter of 2–3 μm. In the precipitation process, it traps and microencapsulates peptides and proteins (e.g., insulin) that are present in the solution during self-assembly. The precipitates are freeze-dried and become a light powder, suitable for pulmonary delivery

to the systemic circulation (Pfützner and Forst 2005; Lim et al. 2016). When administered via the pulmonary route, Technosphere™ dissolves in the pH-neutral environment of the deep lung and facilitates the rapid and efficient absorption of the peptide or protein for systemic circulation. The carrier molecules, Fumaryl diketopiperazine, are not metabolized and are instead excreted as ammonium salts in the urine (Pfützner et al. 2002).

There are additional products approved for systemic therapeutic action by pulmonary delivery, including Adasuve® for CNS therapy (Table 2). Adasuve® loxapine inhalation powder is a single-use, breath actuated device. The FDA approved it in 2012 for the acute treatment of agitation associated with schizophrenia or bipolar 1 disorder in adults (Valdes et al. 2014). Adasuve® utilizes a Staccato delivery, which is a unique thermal system to rapidly heat (in 0.5 s) and vaporize into a thin film. This system allows for rapid systemic delivery of loxapine via inhalation through thermally-generated aerosolization of the excipient-free product (Dinh et al. 2010).

Therapeutic bioequivalence guideline for generic products of DPI

Using generic products has been increasing in recent years, primarily as a cost-saving measure in healthcare provision. The asthma/COPD medication market has rapidly expanded its inclusion of high-cost products. With expiration of patent protection of origin products, generic products for Asthma/COPD are necessary to reduce their high healthcare costs (Lavorini et al. 2013). Establishing bioequivalence is essential in development of generic products because it demonstrate equivalence between the generic product and the reference product by bridging of pre-clinical and clinical test performed on the reference product (Dunne et al. 2013; Sapakal and Govindasamy 2015). For oral dosage forms, methodologies to determine bioequivalence are well established. However, for inhaled drugs, there is currently no universally-adopted methodology, and guidance in this area has been subject to debate (Daley-Yates and Parkins 2011).

When administered by orally, the use of pharmacokinetic data obtained in healthy volunteers is established as the primary means of providing clinical data. The data then support claims of bioequivalence for systemically-acting drugs. The support is on the basis that the drug concentration in the systemic circulation is in equilibrium with the concentration at its site of action. With this assumption, bioequivalence testing can rely on three steps: (1) qualitative and quantitative sameness of the active pharmaceutical ingredient and excipients; (2) in vitro dissolution testing; and (3) a human pharmacokinetic study (Daley-Yates and Parkins 2011; Sapakal and Govindasamy 2015). However, the above approach is not appropriate for locally acting inhaled drugs. Drug concentrations in a systemic circulation system do not necessarily reflect the drug concentrations at the site of action in the lungs. Uncertainty about the relationship between the dose delivered to the site of action in the lungs, topical efficacy, and systemic drug concentrations serves as an obstacle to relying on pharmacokinetic data to assess the bioequivalence of topically-acting, orally-inhaled drugs. Therefore, other sources of data must be considered. For better reliability, establishing bioequivalence may rely on the following five steps: (1) qualitative and quantitative sameness of the active pharmaceutical ingredient and excipients; (2) device similarity to ensure the product performance and the patient device interaction is unchanged; (3) in-vitro device performance testing, including emitted fine particle mass dose and particle-size profiling; (4) in-vivo product performance, including lung deposition and systemic pharmacokinetic data; and (5) confirmation of equivalent topical efficacy (Daley-Yates and Parkins 2011; Sapakal and Govindasamy 2015).

EMA guideline

The European Medicines Agency (EMA) has published finalized guidelines on approving a generic inhaler product. The EMA guidelines advocate a step-wise approach to investigate bioequivalence between test and reference products: Step 1 involves an in-vitro comparison of formulations (only acceptable if criteria for formulation and device equivalence have been met); Step 2 compares formulations using lung deposition models (pharmacokinetics and scintigraphy); and Step 3 involves the use of pharmacodynamics and a clinical efficacy study. Importantly, the demonstration of bioequivalence at Step 1 or Step 2 precludes the need for further comparisons. A schematic of this approach is shown in Fig. 2 (Use 2009; Sapakal and Govindasamy 2015). The EMA guidelines also address the problem of needing different requirements depending on the type of inhalation device under investigation and for dry powder inhalers (DPIs). The guidelines instead require consideration of device resistance and inclusion of sufficient in-vitro data to describe the flow deposition characteristics of the products within the range of clinically-relevant pressure drops and/or flow limits (Use 2009; Daley-Yates and Parkins 2011).

In-vitro bioequivalence (Step 1)

Provided that requirements for formulation and device similarity are met, the applicant may submit an "abridged" application that contains only comparative in-vitro data to substantiate a claim of therapeutic bioequivalence with a

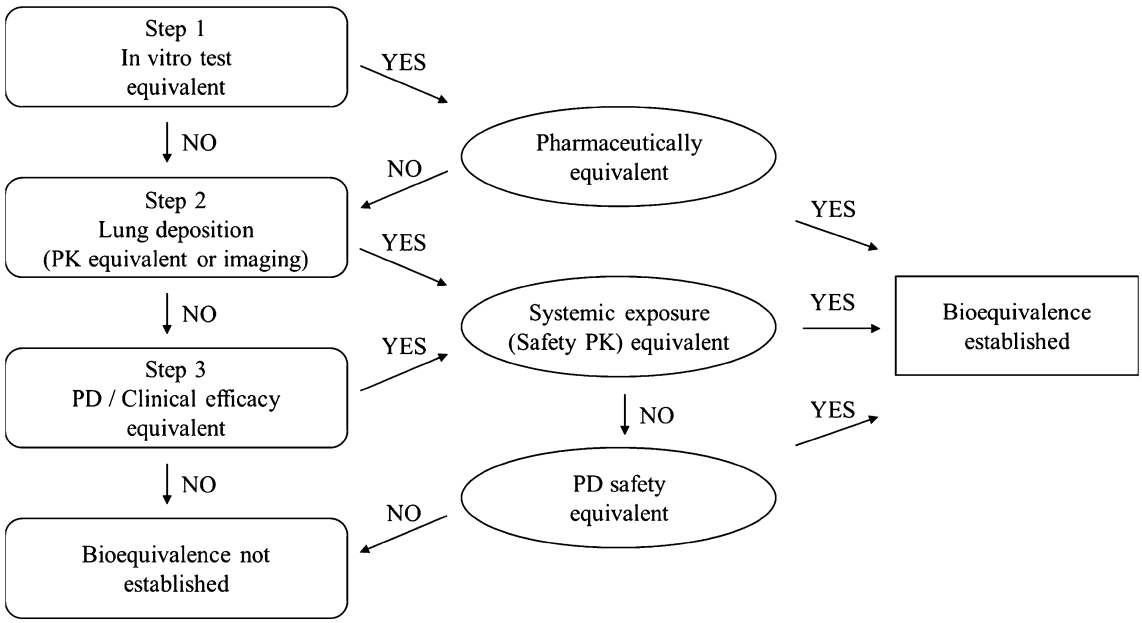

Fig. 2 Schematic of the stepwise approach for establishing bioequivalence advocated by EMA guideline

reference product. If the in-vitro data satisfy specific criteria, the applicants need not provide additional data from clinical pharmacokinetic or efficacy studies. A summary of the criteria from the guideline is presented in Table 3. The interpretation of this aspect of the guideline has been the subject of continuing debate (Use 2009; Daley-Yates and Parkins 2011; García-Arieta 2014; Sapakal and Govindasamy 2015).

Pulmonary deposition bioequivalence (Step 2)

If the in-vitro data do not support a claim of bioequivalence on its face, the next step requires conducting a pulmonary deposition study. Pulmonary deposition studies investigate the extent and pattern of pulmonary deposition of an inhaled active substance. It can be investigated by conducting pharmacokinetic or imaging studies. Pharmacokinetic studies may have some advantages, even though they provide data indirectly from plasma or urine. For example, pharmacokinetic studies are easier to perform, they are safer due to the lack of radiation, they avoid the risk of altering the formulation during radio-labeling, and they can demonstrate linear dose–response relationships more easily. A summary of the key requirements for pharmacokinetic studies are presented in Table 3. Measuring radioactivity in different segments of the lung by using two-dimensional scintigraphic methods can allow for regional quantification of the pulmonary deposition of two products. Equivalent lung deposition of two drugs can be concluded if the 90% confidence interval of the radioactivity in each area is within a range of 0.8–1.25. An equivalent pulmonary deposition demonstrated through imaging studies are regarded as supportive data in respect to therapeutic efficacy. If equivalent pulmonary deposition is shown through imaging studies, this should be followed by appropriate pharmacokinetic studies or appropriate clinical studies to assess therapeutic efficacy. If imaging studies are used instead of pharmacokinetic studies to assess therapeutic efficacy, the grounds on which the studies are being used must be fully justified. Also, it has to be assured that the radio-labelling of the inhaled products has only negligible influence on the deposition characteristics. (Use 2009; Daley-Yates and Parkins 2011; Sapakal and Govindasamy 2015).

Pharmacodynamic and clinical bioequivalence (Step 3)

Clinical therapeutic equivalence is defined as equivalent efficacy and safety when the new inhaled product is compared with an appropriate reference product. Pharmacodynamic and clinical assessments of test and reference products are mandatory when the in-vitro study (Step 1) or pharmacokinetic study (Step 2) fails to demonstrate bioequivalence. EMA guidelines specifically provide appropriate pharmacodynamic methods to determine therapeutic equivalence of inhaled drugs with asthma or COPD indications. If the reference product has an authorized indication that includes both asthma and COPD, therapeutic equivalence studies may only be needed in one of the patient populations to obtain marketing authorization. To investigate therapeutic equivalence of efficacy in inhaled drugs, a pharmacodynamic study requires using two different methods: (1) studies of bronchodilation/

Table 3 EMA guideline regulatory requirements for (a) in vitro bioequivalence and (b) pharmacokinetic bioequivalence

(a) Regulatory criteria leading to the acceptance of in vitro data alone as proof of bioequivalence to a reference medicinal product

- The product contains the same active substance (i.e., same salt, ester, hydrate or solvate, etc.)
- The pharmaceutical dosage form is identical (e.g., pressurized MDI, non-pressurized MDI, DPI, etc.)
- The active substance is in the solid state (powder, suspension) : any differences in crystalline structure and/or polymorphic form should not influence the dissolution characteristics, the performance of the product or the aerosol particle behavior
- Any qualitative and/or quantitative differences in excipients should not influence the performance of the product (e.g., delivered dose uniformity, etc.), aerosol particle behavior (e.g., hygroscopic effect, plume dynamic and geometry) and/or be likely to affect the inhalation behavior of the patient (e.g., particle-size distribution affecting mouth/throat feel or 'cold Freon' effect)
- Any qualitative and/or quantitative differences in excipients should not change the safety profile of the product (within ± 15%)
- Handling of the inhalation devices for the test and the reference products in order to release the required amount of the active substance should be similar
- The inhalation device has the same resistance to airflow (within ± 15%)
- The target delivered dose should be similar (within ± 15%)

(b) Key regulatory requirements for pharmacokinetics studies of orally inhaled drugs in the European Medicines Agency guideline

- The demonstration of bioequivalence for orally inhaled drugs requires that standard criteria be fulfilled, that is, 90% confidence intervals for the log-transformed test/reference C_{max} and $AUC_{(0-t)}$ ratios should lie within 80–125% Tighter limits for AUC and possibly C_{max} may be appropriate for drugs with drugs with a narrow therapeutic index. Widened limits for C_{max} may be acceptable for highly variable products
- Bioequivalence should be confirmed for partial AUC as a measure of early exposure where a rapid onset of effect is important
- Both pulmonary deposition and total systemic exposure should be assessed, unless drug absorption via the oral route is very low such that pulmonary and systemic bioavailabilities are essentially the same
- Total systemic exposure may be acceptable as a surrogate of systemic safety
- Dose selection should be based on pharmacokinetic linearity/nonlinearity
- Both urinary or plasma pharmacokinetic studies are acceptable in adults, whereas in children only the latter are advocated
- Where urinary pharmacokinetic studies are undertaken, plasma C_{max} should be estimated, if feasible, alongside the urinary data
- Pharmacokinetic data for parent compounds/pro-drugs should be presented alongside that of active metabolites, assuming pharmacokinetics of the former are linear and plasma concentrations easily measurable, as C_{max} for parent compounds is more sensitive to detect differences between products
- For pressurized metered dose inhalers, pharmacokinetic data comparing test and reference products in conjunction with spacers should be provided unless comparative in vitro spacer data satisfy stringent criteria for bioequivalence
- For dry powder inhalers, the relevance of differences in intrinsic device resistance should be considered with respect to children

MDI metered dose inhaler, *DPI* dry powder inhaler

assessment of improved airway function; and (2) studies of bronchoprotection. These studies should be carried out in patients who demonstrate reversibility of airway function. The primary outcome variables are forced expiratory volume in 1 s (FEV1), change in FEV1 at appropriate time points, or provocative concentration that produces a 20% fall in FEV1 (PC20 FEV1). To compare the efficacy between test and reference products, two approaches have to be performed. One approach calculates the relative potency, while the other approach compares the results for the pharmacodynamics endpoint for the test and reference products at each dose level studied. In respect to safety, equivalence should be demonstrated by investigation of equivalence based on the pharmacokinetic study (Step 2). Otherwise, equivalence in respect to safety is demonstrated by investigation of equivalence based on relevant cardiovascular, biochemical, and physiological parameters, and monitoring of adverse events. There should be no evidence that the test product is worse than the reference product in respect to changes in vital signs, biochemical parameters, and frequency of adverse events (Use 2009; Daley-Yates and Parkins 2011; Sapakal and Govindasamy 2015).

Conclusion

In order to optimize inhalation therapy, considering the influence of variable airway geometry and the airflow rates through the various regions of the respiratory tract is essential. This review discussed the human respiratory system to understand particle deposition and clearance mechanism during inhalation. Various therapeutic areas of DPIs were introduced, and improvements in formulation and device of DPI were investigated for treatment of local or systemic indications. Bioequivalence of orally inhaled products focused on EMA guidance is finally discussed. This guidance aims to reduce healthcare costs by allowing generic drugs into the market, as patents expire.

An increasing interest in the pulmonary route for both local and systemic acting drugs continues to promote the development of new DPI products. These products provide for new indications, together with new formulations and device technologies. The development of DPIs 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.

Compliance with ethical standards

Conflict of interest All authors (H. Lee, D. Kim, C. Park) declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human or animal subjects performed by any of the authors.

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