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Review

The impact of pulmonary diseases on the fate of inhaled medicines—A review

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ABSTRACT

The portfolio of compounds approved for inhalation therapy has expanded rapidly for treatment of lung diseases. To assess the efficacy and safety of inhaled medicines, a better understanding of their fate in the lungs is essential; especially in diseased lungs where changes in anatomical structure, ventilation parameters and breathing pattern may occur. In this article, the impact of lung pathophysiology factors on the fate of inhaled medicines is reviewed, and discussed in the context of aerosol deposition, dissolution, absorption and clearance. Special emphasis is given to computational modeling of aerosol deposition and clearance taking disease factors into consideration. In silico modeling can be used as a valuable tool to characterize the biopharmaceutics and pharmacodynamics of inhaled medicines, or assess risks associated with inhaled environmental pollutants for patients with pulmonary diseases. The deposition pattern of aerosol particles is greatly altered by different lung diseases based on both experimental data and model simulation. The fate of inhaled medicines after deposition primarily depends on the site of aerosol deposition. Therefore, when developing inhalation products for treatment of lung diseases, the dosing regimen, safety and pharmacokinetic studies should be conducted on patients with lung diseases, in addition to healthy subjects.

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1. Introduction

Treatment of lung diseases by drug inhalation has a long history beginning in the early 1950s when the first inhaled drug for asthma therapy emerged. Over the past 60 years, significant inhalation products have been developed not only for the treatment of asthma, but also for other pulmonary diseases, such as chronic obstruction pulmonary diseases (COPD), cystic fibrosis, pneumonia, to name a few. The rationale for such treatments includes more localized and targeted delivery with minimum systemic exposure. More recently, systemic delivery of drugs administered by inhalation has gained attention due to advantages including: (1) enormous surface area of the lungs; (2) good epithelial permeability; (3) extensive

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Table 1a
Current inhaled pharmaceuticals for treatment of lung diseases on the market or undergoing clinical studies.

Therapeutic usage	Drug classifications	Drugs	Inhalation device	Current development status
COPD and asthma	Short-acting beta-2 agonist (SABAs)	Salbutamol (albuterol)	Nebulizer, pMDI, DPI	Marketed
		Fenoterol	pMDI	Marketed outside of US
		Pirbuterol	Nebulizer, pMDI	Discontinued by Dec.2013
		Terbutaline	DPI	Marketed
		Levalbuterol	pMDI	Marketed
	Long-acting beta-2 agonist (LABAs)	Salmeterol	pMDI, DPI	Marketed
		Formeterol	pMDI, DPI	Marketed
		Arformoterol	Nebulizer	Marketed
		Indacaterol	DPI	Marketed
	Anticholinergic agents	Ipratropium bromide	Nebulizer, pMDI	Marketed
		Tiotropium bromide	pMDI, DPI	Marketed
		Aclidinium bromide	DPI	Marketed
		Oxitropium bromide	pMDI	Outside of US
		Glycopyrronium bromide	DPI	Outside of US
	Inhaled corticosteroids (ICS)	Beclomethasone dipropionate	Nebulizer, pMDI, DPI	Marketed
		Budesonide	Nebulizer, DPI	Marketed
		Fluticasone propionate	pMDI, DPI	Marketed
		Mometasone furoate	pMDI, DPI	Marketed
		Ciclesonide	pMDI	Marketed
	Combination therapy	Fenoterol/Ipratropium	pMDI	Marketed
		Salbuterol/Ipratropium	pMDI	Marketed
		Formeterol/Budesonide	pMDI, DPI	Marketed
		Formeterol/Mometasone	DPI	Marketed
		Salmeterol/Fluticasone	pMDI, DPI	Marketed
		Glycopyrronium/formoterol	pMDI	Phase II
	Sugar alcohol	Mannitol	DPI	Marketed
	Antisense	AIR-645	Nebulizer	Phase II
	Oligonucleotides	PXSTPI-1100	Nebulizer	Preclinical
		ATL-1102	Nebulizer	Preclinical
	CpG oligonucleotides	QAX-935 (IMO-2134)	Nebulizer	Phaes I
	siRNA	Excellair	Nebulizer	Phase II
Cystic fibrosis	Antibiotics	Tobramycin	Nebulizer, DPI	Marketed
		Aztreonam	Nebulizer	Marketed
		Colistimethate sodium	Nebulizer	Pilot trials
		Liposomal ciprofloxacin	Nebulizer	Phase II
		Liposomal amikacin	Nebulizer	Phase III
		Levofloxacin	Nebulizer	Phase III
		PUR118	DPI	Phase I
	Mucous mobilizers	Dornase alfa	Nebulizer	Outside of US
		Lancovutide	Nebulizer	Phase II
	Restore Airway Surface Liquid	Hypertonic saline	Nebulizer	Marketed
		Mannitol	DPI	Phase III
	Antiproteases	Alpha$_1$-antitrypsin	Nebulizer	Phase II
	MRSA lung infections	Vancomycin	DPI	Phase II
Respiratory distress syndrome	Pulmonary surfactant	Phospholipids/surfactant proteins	Endo-tracheal tube	Marketed
Respiratory Syncytial Virus	Antiviral	MDT-637	Novel inhaler	Phase II

There are more than 70 pipeline medicines in development for asthma and more than 50 pipeline medicines in development for COPD. For more information, please refer to Medicines in Development Asthma 2012 report and Medicines in Development COPD 2012 report presented by Pharmaceutical Research and Manufacturers of America (available on PhRMA's web site).

Table 1b
Current inhaled pharmaceuticals for systemic application on the market or undergoing clinical studies.

Therapeutic usage	Drug classifications	Drugs	Inhalation device	Current development status
Analgesia	Opioids	Fentanyl	Novel inhaler	Phase II
		Liposomal fentanyl	Nebulizer	Phase II
Migrane	Triptan	Sumatriptan	Intranasal powder	Phase III
Diabetes	Peptides	Insulin	DPI	Phase III
		Glucagon-like peptide	DPI	Phase I
Nerve gas poisoning	Nerve agent antidote	Atropine	Novel inhaler	Phase I
Parkinson's disease	Psychoactive drug	Levodopa	DPI	Phase II
Schizophrenia	Antipsychotic medication	Loxapine	DPI	Outside of US

DPI, dry powder inhaler; pMDI, pressurized Metered Dose Inhaler. Adapted with permission from Ungaro et al. *J Pharm Pharmacol* 64, 1217–1235 (2012). Other sources are from Global Initiative for Chronic Obstructive Lung Disease (GOLD) web site, Global Initiative for Asthma (GINA) web site and http://clinicaltrials.gov/.

vascularization; (4) faster onset of action compared to the oral route; (5) avoidance of first pass metabolism (Patton and Byron, 2007). Therefore, a variety of inhalation products are under development for treatment of systemic diseases.

Table 1 briefly summarizes the current inhalation products on the market or undergoing clinical studies, their drug classification and therapeutic usage (GINA, 2012; GOLD, 2012; Ungaro et al., 2012). As listed in this table, majority of the