Expert Opinion

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New treatments for chronic obstructive pulmonary disease and viable formulation/device options for inhalation therapy

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Chronic obstructive pulmonary disease (COPD) is an increasingly important cause of morbidity and mortality, pathological features of which are pulmonary inflammation and irreversible airflow obstruction. Current therapies for COPD are aimed at improvement of clinical symptoms and reduction of inflammation in the respiratory systems. There is a pressing need for the development of new COPD medication, particularly as no existing treatment has been shown to reduce disease progression. In spite of a better understanding of the underlying disease process, there have been limited advances in the drug therapy of COPD, in contrast to the enormous advances in asthma management. Several new therapeutic targets and strategies have been proposed, and new drug candidates, including bronchodilators, protease inhibitors anti-inflammatory drugs and mediator antagonists, are now in clinical development for COPD treatment. New dry powder inhaler (DPI) systems for inhaled COPD therapy have also been developed to maximize drug concentrations in the airway systems, while minimizing systemic exposure and associated toxicity. This article aims to review recent developments in COPD drugs and the delivery systems for inhalation therapy, with particular emphasis on device options and formulations of DPI systems.

Keywords: asthma, chronic obstructive pulmonary disease, dry powder inhaler, inhaler device, pulmonary delivery

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is now the fifth leading cause of death worldwide [1], and recent clinical studies have suggested that the prevalence could be as high as 9 – 10% of adults over age 40 [2]. Exacerbations in subjects with COPD are a major cause of mortality and it has been estimated that 10 – 30% of the most severely afflicted will die following hospitalization [3]. COPD is predicted to become the third most common cause of death and the fifth most common cause of disability in the world by 2020 [4]. In spite of major advances in the understanding and management of asthma, COPD has been relatively neglected, and there are no current therapies for reducing the inevitable progression of this disease. As a result of the enormous burden of disease and escalating healthcare costs, exceeding those of asthma more than threefold, there is now renewed interest in the underlying cellular and molecular mechanisms and a search for new therapies [5]. COPD can be subdivided into three distinct pulmonary disorders: chronic bronchitis, small airway disease and emphysema. The lung pathology of COPD is complex and heterogeneous, comprising pulmonary inflammation, small airway

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remodeling, emphysema and mucous hypersecretion [6]. Although current therapy for COPD has improved the management of this difficult disease, there is still a pressing need for new therapeutic approaches, particularly in reducing the progression and mortality of this disease.

Recently, antagonists for muscarinic receptor have been approved and used for treatment of COPD with the aid of inhalation technologies, including inhalation device and powder engineering [7]. In addition, inhaled corticosteroids and long-acting β-agonists (LABAs) are also used in the management of asthma and COPD. In these drugs, balance between the desired effects in the lung and the undesired side effects after systemic circulation is a key consideration that needs to be efficacious and safe. Some asthma drugs such as corticosteroids and β_2-adrenoreceptor agonists were initially available only as oral formulations. Today, oral formulations are used only in specific cases as they are hampered by their side effects [8]. The dominant route of administration for corticosteroids and β-agonists is therefore oral inhalation, as topical application of these drugs to the lung maximizes their efficacy and minimizes potential side effects. The development of inhalable formulations for these drugs might mean a paradigm shift in airway inflammation diseases.

Generally, inhalation system aims to deliver drugs to the respiratory tract and lung either for the topical treatment or prophylaxis of airway diseases or for systemic absorption in the lung for the treatment of many diseases [9]. For any drug to be delivered to the lungs by inhalation, it has to be formulated as an aerosol. Aerosol preparations are stable dispersions or suspensions of solid materials and liquid droplets in a gaseous medium. Aerosolized drugs are deposited in the airways by gravitational sedimentation, inertial impaction and diffusion. Mostly, larger particles are deposited by the first two mechanisms in the airways, whereas the smaller particles reach the peripheral region of the lungs by diffusion [10]. Therefore, inhalable formulation should be optimized for sufficient drug delivery to the lungs to obtain effective therapeutic responses. For optimal efficacy, drug administration must be reliable, reproducible and convenient. This goal can be achieved by a combination of formulation, metering and inhaler design strategies [11].

In this article, the current literature regarding the development of new drug candidates for COPD medication is reviewed, with emphasis on the biochemical and pharmacological mechanisms. In addition, the pulmonary delivery options for new drug entities are also discussed, including the development of dry powder inhaler (DPI) formulations and selection of an appropriate device for aerosol dispersion.

2. COPD and medications

2.1 Characteristics of COPD

2.1.1 *Pathophysiology*

The most important risk factor for COPD in the developed world is cigarette smoking [12]. Exposures to dusts, fumes and air pollution particles are also believed to be causative factors for COPD [12]. COPD is characterized by a chronic, slowly progressive airway constructive disorder resulting from a combination of pulmonary emphysema and irreversible reduction in the caliber of the small airways of the lung. Key contributions to the progression of airway obstruction in COPD are an increase in the volume of tissue in the small airway wall, accumulation of mucous exudates and infiltration of the airway wall by cells of the innate and adaptive immune responses [13]. Activation of inflammatory cells, such as neutrophils, macrophages, T cells and mast cells, is thought to be involved in the airway and alveolar remodeling. Neutrophils and eosinophils possess granules containing matrix-degrading proteases, and activated neutrophils also produce reactive oxygen free radicals. These proteases and free radicals can damage the epithelium and underlying basement membrane in the pulmonary tissues, although this is normally followed by a partial repair process with secretion of antiproteases [14]. Activated macrophages, T cells and mast cells also produce and secrete matrix metalloproteases (MMP), leading to damage on the epithelial barrier. In addition to these inflammatory responses, increased numbers of apoptotic alveolar, bronchiolar and endothelial cells were observed in lung tissues from patients with COPD [15]. A large number of lymph follicles, observed in lung tissues from patients, are responsible for T cell-mediated immune response, leading to apoptotic cell death.

2.1.2 *Differences between bronchial asthma and COPD*

As well as COPD, asthma is one of the most common respiratory diseases, and it is thought that an estimated 40 million asthma patients in the US, Canada, Western Europe and Japan are in need of treatment [16]. Although COPD and asthma both involve inflammation in the respiratory tract, there are marked differences in the nature of the inflammatory process, with differences in inflammatory cells, mediators, response to inflammation and anatomical distribution (**Table 1**) [17,18]. However, COPD and asthma share some clinical features, such as airway obstruction and inflammation. Asthma is a chronic disease characterized by airway inflammation, caused by inhaled allergens and fungal infection (especially *Aspergillus* and *Alternaria* species), that causes variable degrees of both airflow obstruction and airway hyper-responsiveness [19,20]. Histopathological studies on patients with COPD demonstrated a predominant involvement of peripheral airways and lung parenchyma, whereas asthma involves inflammation only in all airways. Many of the inflammatory events in asthma are thought to be mediated by T-helper type 2 lymphocytes (T_H2 cells), as well as mast cells, eosinophils and mesenchymal cells. Whole allergens are presented to T cells, resulting in T-cell activation and elaboration of cytokines [21]. In a type I allergic reaction, immunoglobulin E (IgE) is produced, which is fixed to the mast cell through an Fcε receptor. Crosslinking

Table 1. Clinical and pathologic features of asthma and COPD.

	Asthma	COPD
Age	Any age; many younger	Older
Family history	Common	Uncommon
Symptoms	Exacerbations/remissions	Chronic (if present)
Pathological lesions	Airways	Small airways Pulmonary tissues
Causative factor	Inhaled allergens Fungal infection	Cigarette smoke
Inflammatory cells	T_H2 cell Mast cell Eosinophil Neutrophil	T_H1 cell Alveolar macrophage NeutrophilEosinophil
Mediators	IL-4, IL-5, LTD_4, IgE	IL-8, TNF-α, LTB_4, MCP-1
Pathophysiological change	Bronchoconstriction Eosinophilic inflammation Antibody production	Alveolar wall destruction (Emphysema) Mucus hypersecretion (Chronic bronchitis) Small airways fibrosis

COPD: Chronic obstructive pulmonary disease.

of allergen-specific IgE leads to the release of the inflammatory mediators, including cytokines, chemokines, adhesion molecules, proteinases and growth factors, which participate in this process at various stages and interact to maintain and amplify the inflammatory response [22]. On the contrary, marked infiltration of macrophages, T-helper type 1 lymphocytes (T_H1 cells) and neutrophils was observed in COPD patients [5], and eosinophils are not prominent, unlike in asthma. There are several chemotactic signals that have the potential for recruitment of inflammatory cells in COPD, such as leukotriene B_4 (LTB_4), interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1) and related CXC chemokines, which are increased in COPD airways. These mediators may be derived from alveolar macrophages and epithelial cells, but the neutrophil itself is a major source of IL-8. Thus, COPD and asthma are two distinct disorders with different origins, natural history and outcomes, and certainly require different therapeutic approaches.

2.2 Current medications for COPD and asthma

2.2.1 COPD therapy

The aims of COPD medication are to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and improve exercise tolerance [6]. Prevention of the accelerated decline in lung functions would reduce mortality, and reducing the frequency and severity of exacerbations is an increasingly important target therapy. Current COPD therapies focus mainly on reducing symptoms using short-acting and long-acting bronchodilators (**Table 2**). Three classes of bronchodilators, including β_2-adrenoceptor agonists, anticholinergics and methylxanthines, are now available and can be used individually or in combination, for example, long-acting β_2-adrenoceptor agonist bronchodilators with inhaled corticosteroids. Bronchodilators are the mainstay of pharmacologic therapy for COPD, and are recommended by current national and international guidelines as first-line therapy in symptomatic patients and those who demonstrate airflow limitation [23].

2.2.2 Bronchodilators

Short-acting β_2-aderenoceptors (SABAs), such as albuterol, have a rapid onset of action, and are very effective for the rescue of symptoms in COPD. In addition to their bronchodilatory properties, these agents are effective at increasing mucociliary clearance. LABAs, including salmeterol and formoterol, have been shown to improve significantly lung function, health status and symptom reduction. In particular, formoterol has fast onset of action, therefore it has a potential role as standalone medication or in combination with another bronchodilator in the management of acute COPD exacerbation and for use as a rescue and maintenance medication [23,24]. Short-acting agents are usually used for immediate relief of symptoms, whereas long-acting inhaled agents are generally preferred and are more convenient.

In the pathogenesis of COPD, increased cholinergic tone is important, contributing both to increased bronchial smooth muscle tone and to mucus hypersecretion [25]. Thus, anticholinergics, including ipratropium bromide and tiotropium, reduce airway tone and improve expiratory flow limitation, hyperinflation and exercise capacity in patients with COPD. The short-acting ipratropium has long been used as monotherapy or in combination with albuterol in COPD medication. However, recent clinical reports have indicated that the use of long-acting tiotropium as a dry powder inhaler is superior in improving health outcomes, such as health status, dyspnea and exercise capacity [26].

Table 2. Current medications for asthma and COPD*.

Drug	Application	Administration routes
β stimulants		
Salbutamol	Asthma	Oral, inhalation (pMDI, nebulizer)
DL-Methylephedrine	Asthma	Oral, injection, suppository
DL-Isoprenaline	Asthma	Oral, inhalation (pMDI)
Orciprenaline	Asthma	Oral, injection, inhalation (nebulizer)
Tulobuterol	Asthma	Oral, transdermal
Procaterol	Asthma	Oral, inhalation (nebulizer, pMDI, DPI/Clickhaler)
Fenoterol	Asthma	Oral, inhalation (pMDI)
Formoterol	Asthma	Oral, inhalation (DPI/Aerolizer)
Salmeterol	Asthma	Inhalation (DPI/Discus or Rotadisk)
Steroids		
Prednisolone	Asthma	Oral
Betamethasone	Asthma	Oral, injection, inhalation (nebulizer)
Dexamethasone	Asthma	Oral
Budesonide	Asthma	Inhalation (nebulizer, DPI/Turbuhaler)
Beclomethasone dipropionate	Asthma	Inhalation (pMDI)
Fluticasone propionate	Asthma	Inhalation (pMDI, DPI/Discus or Rotadisk)
Ciclesonide	Asthma	Inhalation (pMDI)
Methylxanthine		
Theophylline	Asthma, COPD	Oral
Chemical mediator release inhibitors		
Sodium cromoglicate	Asthma	Inhalation (nebulizer, pMDI, DPI/Spinhaler)
Tranilast	Asthma	Oral
Repirinast	Asthma	Oral
Ibudilast	Asthma	Oral
Pemirolast	Asthma	Oral
Histamine blockers		
Ketotifen	Asthma	Oral

*Not all listed compounds in the table are available in all countries.
COPD: Chronic obstructive pulmonary disease; DPI: Dry powder inhaler; pMDI: Pressurized metered dose inhalers.

Table 2. Current medications for asthma and COPD* (continued).

Drug	Application	Administration routes
Azelastine	Asthma	Oral
Epinastine	Asthma	Oral
Thromboxane synthetase inhibitors		
Ozagrel	Asthma	Oral
Thromboxane antagonists		
Seratrodast	Asthma	Oral
T_H2 cytokine inhibitor		
Suplatast	Asthma	Oral
Leukotriene receptor antagonists		
Pranlukast	Asthma	Oral
Zafirlukast	Asthma	Oral
Montelukast	Asthma	Oral
Muscarine receptor antagonists		
Tiotropium bromide	COPD	Inhalation (DPI/Handihaler)
Ipratropium bromide	COPD	Inhalation (nebulizer, pMDI)
Combo		
Salmeterol/fluticasone propionate	Asthma	Inhalation (DPI/Discus)
Formoterol/budesonide	Asthma	Inhalation (pMDI, DPI/Turbuhaler)
Isoprenaline/atropine methylbromide/dexamethasone	Asthma	Inhalation (pMDI)

*Not all listed compounds in the table are available in all countries.
COPD: Chronic obstructive pulmonary disease; DPI: Dry powder inhaler; pMDI: Pressurized metered dose inhalers.

Methylxanthines, such as theophylline, act as non-selective phosphodiesterase (PDE) inhibitor, providing weak bronchodilation and respiratory stimulation. PDE enzymes catalyze the metabolism of cAMP, therefore inhibition of PDE by theophylline results in an increase in intracellular cAMP levels, providing both bronchodilatory and anti-inflammatory activities [27]. However, it has potential adverse effects and narrow therapeutic index, so it should be used only when symptoms persist despite optimal bronchodilator therapy. At present, several PDE4 inhibitors are in various stages of development.

Combinations of bronchodilators might improve efficacy and reduce risk of adverse effects rather than increasing the dose of a single agent. In particular, the use of an inhaled anticholinergic agent with a β_2-adrenoceptor agonist seems to be a convenient way of delivering treatment and obtaining better results. The physiologic and clinical benefits of LABAs can be enhanced when administered in conjunction with inhaled corticosteroids. Emerging evidence from *in vitro* studies also suggests an interaction between corticosteroid and muscarinic receptors, which may provide a rationale for use of anticholinergic/corticosteroid combination therapies [28].

2.2.3 *Corticosteroids*

Severe inflammation of the airways, followed by marked invasion of neutrophils, is a characteristic feature of COPD, as well as severe asthma; so glucocorticoids are widely prescribed for COPD with the aim of anti-inflammation. However, long-term clinical trials with high doses of inhaled glucocorticoids in the treatment of stable COPD have been disappointing, as they do not appear to arrest the progressive decline in lung function, even when treatment is started before the disease becomes symptomatic [29]. Although inhaled corticosteroids are highly effective in asthma, they provide little benefit in COPD, despite the fact that airway and lung inflammation are present. The lack of reduction in inflammatory cells, cytokines, or proteases in induced sputum after oral administration of corticosteroids speaks well of the absent response of inflammation to these agents in COPD. The lack of response to corticosteroids may be explained, at least in part, by an inhibitory effect of cigarette smoking and oxidative stress on histone deacetylases, thus interfering with a critical anti-inflammatory action of corticosteroids [30].

2.2.4 *Antiasthma drugs*

Some COPD drugs have been clinically used for treatment of asthma as well. Current asthma therapies come in two categories: bronchodilators and anti-inflammatory drugs (**Table 2**). Like COPD, the main treatment for acute asthma attacks is SABAs, showing a rapid onset of action and bronchodilatory effect by relaxing the airway smooth muscle and decreasing airway resistance. The realization that asthma is an inflammatory disease shifted the focus of its treatment from bronchodilators to anti-inflammatory drugs. The anti-inflammatory drugs, including corticosteroids, chemical mediator release inhibitors, antiallergenics, thromboxane inhibitors and immunosuppressors, are mainly long-term medications and are aimed at the treatment of airway inflammation and airway hyper-responsiveness. At present, according to Global Initiative for Asthma (GINA) guidelines, the goal of clinical treatment of asthma is to control airway inflammation in order to modify the progression of the disease because this strategy will certainly provide better quality of life to the patient [19]. Despite the availability of a great number of medications, the asthma epidemic, as well as COPD, is continuing to increase. It is obvious that a high, unmet medical need remains and innovative therapeutic agents for COPD and asthma are urgently required.

3. New drug candidates for the treatment of COPD

3.1 Development of new COPD medications

There have been important advances in the understanding of the cellular and molecular biology of COPD, and several new therapies are now in development for COPD (**Table 3**). New therapies for COPD may arise from improvements in existing classes of drug, such as LABA and anticholinergics, or from the development of new therapies based on a better understanding of the underlying disease process (**Figure 1**). Several new therapeutic strategies, such as protease inhibitors, anti-inflammatory agents and mediator antagonists, are aimed at controlling the underlying inflammatory processes of COPD. In the following sections, an attempt is made to highlight the principal activities of the COPD therapy.

3.2 New COPD drug candidates

3.2.1 *Bronchodilators*

Bronchodilators, especially LABAs, are currently recommended as mainstay therapy for COPD. After the discovery of formoterol and salmeterol, there has been a renewed interest in the development of new candidates of LABAs in recent years. Once-daily β_2-adrenoceptor agonists or ultra-LABAs are in development in an attempt to simplify COPD management [31]. In particular, GSK-159797 (TD-3327) is an ultra-LABA for the potential once-daily treatment of COPD [32], and it achieved the target increase in forced expiratory volume in 1 s (FEV_1) throughout the 24-h evaluation period in a study of 38 patients [33]. Most of these agents have a high intrinsic efficacy and a quick onset of action, as well as longer duration of action, and may have advantages leading to improved overall clinical outcomes in patients with COPD.

In addition to ultra-LABAs, agonists for vasoactive intestinal peptide (VIP) receptors, including [$R^{15,20,21}$, L^{17}]-VIP-GRR (IK312532) and acetyl-[E^{8}, $K^{12,27,28}$, Nle^{17}, A^{19}, D^{25}, L^{26}, $G^{29,30}$, T^{31}]-VIP(cyclo 21 – 25) (Ro 25-1553), are believed to be promising candidates of COPD and asthma owing to their potent bronchodilation and anti-inflammatory effects [34].

Table 3. New drug targets and candidates for COPD treatments.

Candidates	Developmental	Developers	Ref.
Bronchodilators			
Ultra long-acting β_2-adrenoreceptor agonists			
GSK-159797	Phase II	GlaxoSmithKline	[23,33]
Arformoterol	Approved	Sepracor	[23,33]
VPAC receptor agonists			
IK312532	Preclinical	Ito Life Sciences American Peptide	[34]
Protease inhibitor			
Elastase inhibitors			
BAY719678	Phase I	Bayer	[6]
Recombinant α_1-antitrypsin	Phase II	Baxter	[6]
MMP inhibitors	Discovery stage		[38-40]
Cathepsin inhibitors	Discovery stage		[36,39,40]
Anti-inflammatory agents			
PDE4 inhibitors			
Roflumilast	Phase III	Altana	[6,42]
Cilomilast	Phase III	GlaxoSmithKline	[6,42]
G3193	Phase II	Merck	[6]
Tetomilast (OPC6535)	Phase II	Otsuka	[6]
Tofimilast	Phase II	Pfizer	[6]
Adenosine receptor agonists			
UK-432097 (A_{2A})	Phase II	Pfizer	[44]
GW328267X (A_{2A})	Phase II	GlaxoSmithKline	[44]
Adenosine receptor antagonist Adenosine receptor agonists			
CVT-6883 (A_{2B})	Phase I	CV Therapeutics	[44]
5-Lipoxygenase inhibitor			
PEP03	Phase II	PharmaEngine	[6]
p38 MAPK inhibitors			

COPD: Chronic obstructive pulmonary disease.

Table 3. New drug targets and candidates for COPD treatments (continued).

Candidates	Developmental	Developers	Ref.
GSK-856553	Phase I	GlaxoSmithKline	[46]
BIRB-796	Phase II	Boehringer	[46]
IKK2 inhibitors			
IMD1041	Phase I	IMMD	[6]
MLN0415	Phase I	Millennium	[6]
NF-κB inhibitors	Discovery stage		[39,40,50]
Mediator antagonists			
TNF-α inhibitors			
Infliximab	Phase II	Centocor	[6,39,40]
Etanercept	Phase II	Wyeth	[6,39,40]
IL-1 inhibitor			
Monoclonal antibody to IL-1	Phase I	Novartis	[6]
iNOS inhibitors			
GW-274150	Phase II	GlaxoSmithKline	[6,48]
SC-51	Phase I	Pfizer	[6,49]
Chemokine receptor (CXCR2) antagonists			
SCH527123	Phase I	Schering Plough	[6,47]
AZD8309	Phase I	AstraZeneca	[6]

COPD: Chronic obstructive pulmonary disease.

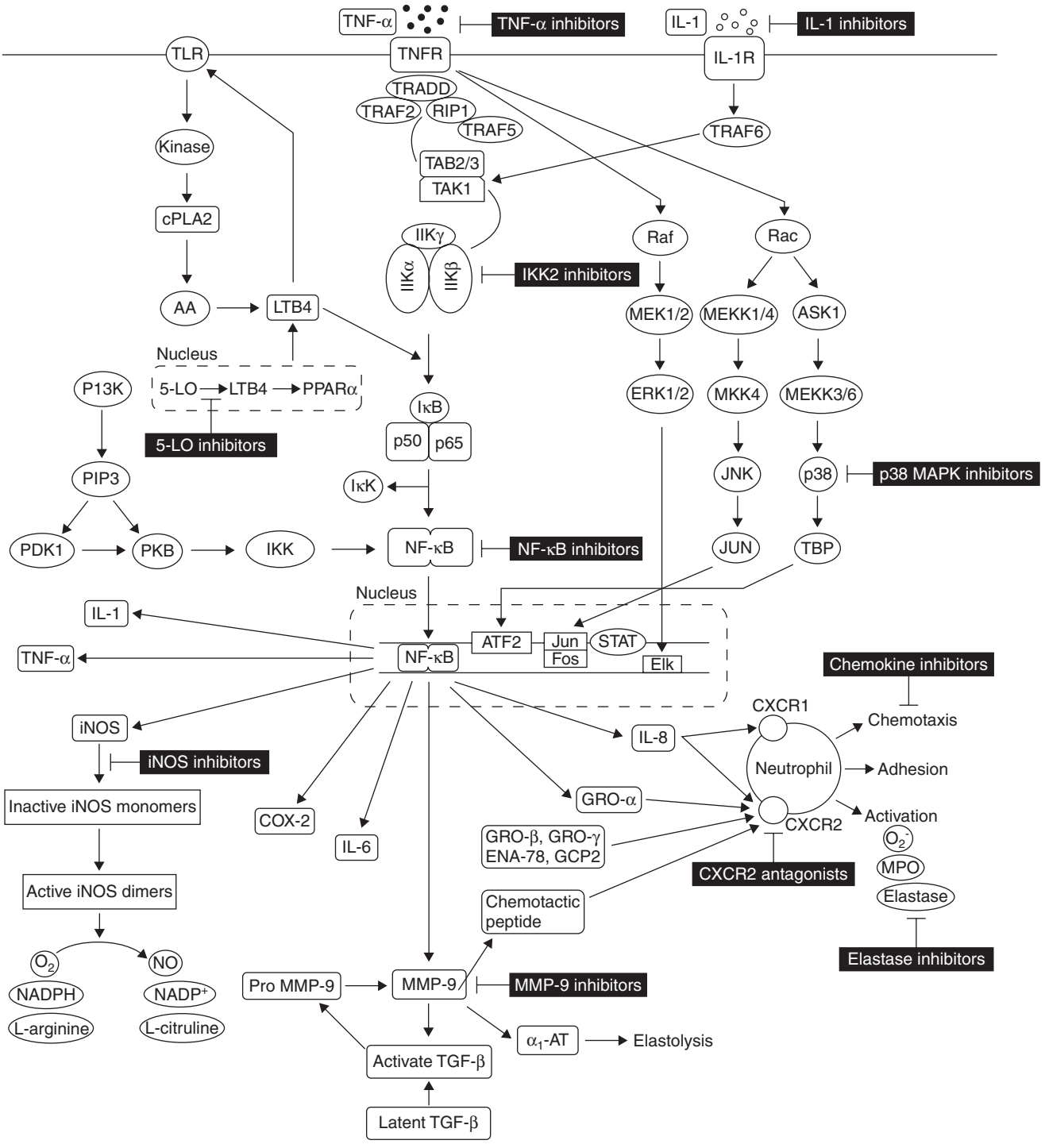

Figure 1. Schematic summary of airway inflammation in COPD and potential therapy by blocking toxic cascades.

5-LO: 5-lipoxygenase; α_1-AT: α_1-Antitrypsin; AA: Arachidonic acid; ASK1: Apoptosis signal-regulating kinase 1; ATF2: Activating transcription factor 2; cPLA2: Cytosolic phospholipase A_2; COX-2: Cyclooxygenase 2; CXCR: Receptor for cysteine-X-cysteine chemokines; ENA-78: Epithelial neutrophil-activating peptide-78 (CXCL5); Elk: Ets(E26)-like kinase; ERK1/2: Extracellular signal-regulated kinase-1/2; GCP2: Granulocyte chemotactic protein 2; GRO-α: Growth-related oncogene-α (CXCL1); IκB: Inhibitor of κB kinase; IKK: Inhibitors of IκB kinase; IL-8: Interleukin-8 (CXCL8); JNK: c-Jun N-terminal kinase; LTB_4: Leucotoriene B_4; MEK: MAPK/ERK kinase; MEKK: MEK kinase; MKK: MAPK kinase; MMP-9: Matrix metalloprotease-9; MPO: Myeloperoxidase; NF-κB: Nuclear factor κB; PI3K: Phosphatidylinositol 3-kinase; PDK1: Phosphoinositide-dependent kinase 1; PIP3: Phosphatidylinositol triphosphate; PKB: Protein kinase B; PPARα: Peroxisome proliferator activated receptor-α; RIP: Receptor interacting protein; STAT: Signal transducer and activator of transcription; TAB: TAK1-binding protein; TAK: TGF-β-activated kinase; TBP: TNF binding protein; TGF-β: Transforming growth factor-β; TLR: Toll-like receptor; TNF: Tumor necrosis factor; TNFR: TNF receptor; TRADD: TNF receptor-associated death domain; TRAF: TNF receptor-associated factor.

Although the precise role of VIP in the pathogenesis of asthma and COPD is still uncertain, a VIP deficiency in the airways of severe asthmatic patients has been reported [35]. Therein, a hypothesis was proposed that VIP deficiency might lead to the bronchial hyper-reactivity on the basis that VIP acts most probably as a neurotransmitter, the dominant mechanism of human airway relaxation. These findings also suggested that deficiency of the *VIP* gene may cause a predisposition to the pathogenesis, and therefore treatment with VIP or its derivatives may offer potentially effective replacement therapy for the disease.

3.2.2 *Protease inhibitors*

Imbalance between proteases and antiproteases contributes to proteolytic damage in the lung, leading to emphysema, and it is one of the pathophysiological features of COPD. So, inhibition of proteases and enhancement of antiproteases are emerging therapeutic strategies in COPD medication, with the aim of reduction in tissue damage with concomitant impairment of disease progression [36]. Neutrophil elastase inhibitors have been suggested as new therapeutic agents to prevent further damage in the lungs of patients with COPD. Different classes of elastase inhibitor are being evaluated in preclinical and clinical trial, which include BAY719678 and recombinant α_1-antitrypsin for inhalation therapy.

Elastase increases MMP activity by directly activating MMPs such as MMP-9 and by inactivating the endogenous MMP inhibitor, termed tissue inhibitor of matrix metalloproteinases (TIMP-1) [37]. MMPs are produced by many inflammatory cells, and they have been considered as vital mediators of inflammation in pulmonary diseases, including asthma and COPD. Therefore, inhibition of these proteases is also being evaluated as a therapeutic target in COPD. However, little is known regarding the clinical efficacy of MMP inhibitors in COPD [38]. In addition to MMP inhibitors, inhibition of cathepsins could be a therapeutic option in COPD medication [36]. Cathepsins K, L and S, released from macrophages, are members of the cysteine proteinase family, levels of which are found to be elevated in the airways of patients with COPD. Cathepsins cleave and inactivate secretory leukocyte protease inhibitor (SLPI), thereby increasing the proteolytic burden. On the basis of cell biology of cathepsin, some cysteine-protease inhibitors have drawn attention as being new targets of COPD drugs, which might prevent progression of airway obstruction [36,39,40].

3.2.3 *Anti-inflammatory drugs*

Unfortunately, clinical trials suggested that inhaled corticosteroids have no benefit on the rate at which lung function declines in COPD. The current concepts of COPD pathogenesis accelerate the alternative anti-inflammatory strategies for COPD medication. With the current understanding of the complexity of the inflammatory process, there are hundreds of potential therapeutic targets with potential relevance for COPD (**Figure 1**) [41]. Pulmonary inflammation could be reduced by blocking accumulation of inflammatory cells and systemic effects of inflammation, with new classes of anti-inflammatory chemicals.

Several strategies have been suggested to block the inflammatory cell accumulation, and they were targeted to block the following steps of inflammatory cells: production; release into the circulation; emigration from the circulation; recruitment into tissues; activation; elimination; and residence in tissues. PDE4 inhibitors could block several steps involved in inflammatory cell recruitment, resulting in marked reduction of inflammatory cell accumulations [41,42]. Preclinical studies show that PDE4 inhibitors suppress a wide variety of inflammatory effects both *in vitro* and *in vivo*, and clinical trials in COPD are continuing [36]. In particular, two new drug entities are now in advanced development, roflumilast and cilomilast [6]. Despite being well tolerated in the clinical study, there is concern that the effectiveness of PDE4 inhibitors may be limited by adverse effects, most notably nausea and gastrointestinal upset [43]. In addition to PDE, adenosine mediates a variety of cellular inflammatory responses relevant to asthma and COPD through interaction with specific receptors (A_1, A_{2A}, A_{2B} and A_3). A_{2A} receptor agonists prevent the infiltration of inflammatory cells into the lung and thus may be of therapeutic use [44]. Highly potent A_{2A} receptor agonists, including UK-432097 and GW328267X, are in clinical development, but potential problems may result from cardiovascular side effects with these agents. A_{2B} receptor antagonists, such as CVT-6883, prevent degranulation of mast cell and the overproduction of pro-inflammatory cytokines and extracellular matrix by smooth muscle cells, bronchial epithelial cells and pulmonary fibroblasts.

The 5-lipoxygenase (5-LO) pathway of arachidonic acid metabolism generates leukotrienes (LTs), and LTB_4 acts as a potent neutrophil chemoattractant and extends neutrophil survival [45]. The elevated levels of LTs are associated with COPD pathogenesis, so 5-LO inhibitors could be effective for attenuating pulmonary neutrophilia in COPD. Although 5-LO inhibitors have been in development, the incidence of adverse effects is limiting development of these drug candidates. Recently, PEP03 was developed as a highly selective, potent and orally active 5-LO inhibitor. Preclinical pharmacological *in vitro*, *ex vivo* and *in vivo* testing indicated that PEP03 has multiple beneficial actions, including prevention of bronchoconstriction, and reduction of vascular leakage, cellular infiltration and bronchial hyper-responsiveness [6].

NF-κB regulates the expression of IL-8 and other chemokines, as well as TNF-α and some MMPs, therefore there are several approaches to the inhibition of NF-κB, including orally available NF-κB inhibitors, gene transfer of the inhibitors of NF-κB, and inhibitors of NF-κB-inducing kinases [39,40]. Some kinases are believed to play a crucial role in the expression and activation of inflammatory mediators in the airway, in T-cell function and airway remodeling. Encouraging data from animal models and primary cells or early clinical studies suggest that inhibitors of p38 mitogen-activated protein

(MAP) kinase and inhibitor of IκB kinase 2 (IKK2) may prove to be useful new therapies in the treatment of severe asthma and COPD [6,46]. In addition to these new drug entities, there are several possibilities for reducing pulmonary inflammation in COPD, either with newly developed anti-inflammatory chemicals [36,41].

3.2.4 *Mediator antagonists*

Several mediators are involved in the inflammatory process in COPD; therefore, blocking individual mediators might have therapeutic potential [7]. Current drug discovery for COPD therapy is focusing on the development of antagonists or inhibitors against nitric oxide (NO), lipid mediators such as prostaglandin (PG) E_2, $PGF_2\alpha$ and LTB_4, and cytokines such as TNF-α, IL-1, TGF-β1 and chemokines. Particularly in patients with COPD, TNF-α plays a key role in amplifying inflammatory responses through activation of NF-κB, activator protein-1 and other transcription factors. In addition, COPD patients with weight loss show increased releasability of TNF-α from circulating cells, eventually leading to apoptosis of skeletal muscle. At present, clinical application of humanized monoclonal antibody directed against TNF-α (infliximab) and soluble TNF-α receptors (etanercept) for COPD medication is underway [6]. However, the use of these biologics for the chronic disease might be challenging, because of their limited administration routes and high cost, so development of orally available drug candidates with low molecular mass is urgently required.

Several chemokines are involved in the chemotaxis and recruitment of granulocytes into the pulmonary tissues of COPD patients [5], and they exert their effects on neutrophils through the activation of chemokine receptors CXCR1 and CXCR2 on the neutrophil surface. Recently, attention has been drawn to the development of selective CXCR2 antagonists, including SCH527123 and AZD8309, and blockade of this receptor inhibits neutrophil recruitment into the lung [47]. Increased NO levels in COPD patients could also be responsible for oxidative stress, and the formation of peroxynitrite might also lead to steroid resistance in COPD through nitration and inactivation of histone deacetylase-2 [30]. Selective inhibitors of NO synthase (iNOS), such as GW-274150 and SC-51, are now in development, and they are effective in COPD-like experimental animal models [48,49]. In addition to these mediators, several toxic or inflammatory mediators are associated with COPD pathogenesis [14,36,50]. The combined use of some mediator antagonists might be necessary for sufficient clinical effects.

3.3 Potential problems in new COPD drug development

Several reasons for the challenges and difficulties of drug development for COPD have been pointed out, including: i) no satisfactory animal models; ii) patients present late in the course of the disease; iii) cell and molecular biology not fully defined; iv) multiple mediators and enzymes involved; v) proof-of-concept studies uncertain; vi) delivery systems not yet optimized; and vii) definitive studies require large patient numbers to be studies over > 3 years [39,40]. Furthermore, little information exists about surrogate biomarkers to monitor the short-term efficacy of new treatments. As well as these challenges, pulmonary drug delivery systems could be a key consideration for clinical application of newly developed COPD drug candidates. At present, bronchodilators are given as metered dose inhaler or dry powder inhalers that have been optimized to deliver drugs to the respiratory tract in asthma. However, to achieve maximal benefit in patients with COPD, a bronchodilator or other drug candidates must be delivered to the small airway using a proper techniques, as the inflammatory and destructive processes takes place in small airways.

4. Dry powder formulations and devices for inhalation therapies

4.1 Inhalation systems: nebulizer, dry powder inhaler and metered dose inhaler

In the treatment of COPD with marketed or new drug entities, as demonstrated by oral steroids and PDE4 inhibitors, systemic side effects might limit the therapeutic dose significantly. However, treatment of COPD with inhaled drugs offers advantages over systemic therapy, including a more rapid onset and reduced adverse effects, because of direct targeting of the airway systems. To achieve maximal benefit, a drug must be delivered correctly to the airway systems using inhalation systems, including nebulizers, pressurized metered dose inhalers (pMDI) and DPI [51]. First, nebulizers come as venturi-jet type or ultrasonic piezoelectric type, and produce an aerosol from a liquid drug solution. The drawbacks of nebulizers include a lack of portability, it is an expensive device, the inconvenience of having to load each dose individually into the device, and the time required to inhale each dose. Nebulizers account for < 1% of the drug delivery devices used by patients. Second, pMDI is composed of a propellant such as hydrofluoroalkanes in a pressurized canister. pMDIs have been the mainstay drug delivery device for medications used in the treatment of asthma and chronic obstructive lung disease. Third, DPI comes in a single dose or multi-dose, and DPI generally relies on the energy of the patient's own inhalation to draw a dose of medication into the lungs [52].

4.2 Choice of inhaler: practical problems

The primary qualifications are that the patient is able to use the device correctly and that the drug is available in the device. The use of multiple inhaler types might lead to confusion for patients, resulting in errors of use. Van der Palen and co-workers previously reported that a higher percentage of subjects showed no inhalation errors when only one inhaler was used, as compared with two or more inhalers [53]. The percentage of patients performing all the essential steps

of inhaler use was greater when a combination of DPIs was used, as compared with a combination of a pMDI and DPI [54]. Although nebulizers are considered to be the easiest inhaler system to use, patient compliance with home nebulizer therapy in COPD was 57% [55]. Misuse of inhaler devices can lead to inadequate drug dosing and suboptimal diseases control. Fink and Rubin reported that 28 – 68% of patients do not use their pMDIs or DPIs well enough to benefit from the prescribed drug, and improper use of inhalers might result in $7 billion – 16 billion being wasted, with no benefit to the patient [56]. Therefore, the choice of the device must be tailored according to the patient's needs, situation and preference, and training and education from healthcare-givers has a key role for improving inhaler technique and compliance.

In the inhalation therapy with the use of nebulizer, drugs should first be solubilized/suspended in an aqueous medium and subsequently aerosolized (liquid aerosolization or nebulization) through a nebulizer. In aqueous solution, significant hydrolysis and other chemical reactions within drugs or excipients might occur. A nebulizer requires little patient cooperation, and can be used at any age for any disease severity or acuity [57]. pMDI became a gold-standard inhaler device soon after its introduction in 1956; however, recognition of the limitations of pMDI as a delivery device, as indicated below, has been a driving force to develop a new DPI [51]. In particular, the ban on the use of chlorofluorocarbon propellants in pMDI for environmental reasons has forced the pharmaceutical companies to seek alternatives. In addition, pMDIs are associated with frequent dosing errors related to the need simultaneously to aim the device towards the oropharynx, press down a mechanism to actuate the high-velocity spray, and slowly inhale the medication. Therefore, the proper use of pMDI requires intensive training by physicians, and regular technique retesting may also be necessary. Actually, the radioisotope studies have shown that only 15% of medication dose delivered using a pMDI is inhaled into the bronchial tubes, with the remainder impacting on the oral mucosa or being exhaled into the environment [58]. In contrast to these propellant-driven devices, all available DPIs are breath-actuated, precluding the need for the patients to adjust actuation with inhalation [59]. In addition, the more recently developed multi-dose DPIs have either a dose counter or an indicator, which tells the patient how much medication remains in the inhaler. At present, DPIs are widely accepted inhalation systems, particularly in Europe where they are now used by an estimated 40% of patients to treat asthma and COPD [60].

4.3 Dry powder inhaler devices

Most DPI systems in current use are passive systems, and they require the energy from inhalation to generate an aerosol. On the contrary, active DPIs use an impeller or other mechanical device to generate inspiratory airflow [61]. A shared problem with both DPIs is that the powdered medication tends to clump, making dosing inconsistent and dispersal of particles too large for optimal inhalation into the bronchial tubes. Particle-to-particle interaction affects the ability of a dry powder medication to redisperse into smaller particles suitable for inhalation. Typically, agglomerated particles of the medication are delivered to the patient, rendering the medication less effective. In addition, particles of a medication have larger forces of inertia, causing them to impact on the oropharynx and subsequently be swallowed rather than being inhaled into the bronchial tubes. Therefore, an objective of the invention is to provide a multiple-dose inhaler device for consistently delivering a measured dosage of a dry powder medication into the lungs of a patient. Other objectives would be to provide: i) an inhaler that eliminates the possibility of patients receiving multiple doses; ii) an inhaler that operates without the use of a propellant; iii) an inhaler that will deliver a dry powder medication as small and separated particles; and iv) an inhaler device that is small, compact and easy for the user to operate. So far, many new DPIs have been developed by pharmaceutical industries (**Table 4**) [60,62-78]. These devices may be characterized as follows: unit-dose device [62-67,79], multiple-unit dose device [68-70], or multi-dose device [60,71-79]. In single-dose devices, doses are individually loaded into gelatin capsules, or possibly into blisters, each of which is loaded into the inhaler immediately before use. Some of the oldest devices fall into this category, for example, Rotahaler (GlaxoSmithKline, Greenford, UK) [62] and Spinhaler (Aventis, Holmes Chapel, UK) [63]. Multiple-unit dose devices contain a series of capsules or blisters, for example, Diskhaler (GlaxoSmithKline) [68] and Flowcaps (Hovione, Lisbon, Portugal) [69]. In multi-dose devices, the drug is metered either from a reservoir of from freely flowing powder, for example, Turbuhaler (AstraZeneca, Lund, Sweden) [73], Easyhaler (Orion, Kuopio, Finland) [60] and Novolizer (Viatris, Frankfurt, Germany) [77]. Multiple-dose devices incorporating powder reservoirs are generally capable of delivering > 100 metered doses, providing a level of convenience equivalent to a pMDI. Multiple-unit dose devices may offer other advantages in terms of more accurate metering of individual doses and better protection against ingress of moisture, but are generally more expensive to produce.

4.4 Powder formulations for dry powder inhaler system

4.4.1 General powder formulations for inhaled therapy

Efficacious delivery from any inhaler devices, especially DPI, depends not only on the inhaler device, but also on the formulation. Although the development of DPI devices has proceeded apace, it was realized in the 1990s that device engineering alone would not solve all inhaled drug delivery problems. There was likely to be mileage in developing sophisticated new powder formulations, where the formulation rather than the device works to ensure efficient and reproducible

Table 4. Dry powder inhalers and their principles for powder de-agglomeration.

Inhalation devices	Dispersion principle	Developers
Unit-dose type		
Rotahaler	Patient's own inhalation	GlaxoSmithKline [62]
Spinhaler	Patient's own inhalation	Aventis [63]
Handihaler	Patient's own inhalation	Boehringer Ingelheim [64]
Aerolizer	Patient's own inhalation	Novartis [79]
Directhaler	Discharge channels	Direct-Haler AS [65]
Jethaler	Cyclone chamber	Hitachi [66]
Inhance	Pressurized air	Nektar [67]
Aspirair	Vacuum chambers	Vectura [65]
Multiple unit-dose type		
Diskhaler	Patient's own inhalation	GlaxoSmithKline [68]
Flowcaps	Patient's own inhalation	Hovione [69]
Spiros	Battery-powered systems	Dura Pharmaceuticals [70]
Multi-dose type		
Diskus	Patient's own inhalation	GlaxoSmithKline [79]
Easyhaler	Venturi effect	Orion Pharma [60]
Clickhaler	Impact bodies	Innovata Biomed [71]
Certihaler	Impact bodies	SkyePharma [72]
Turbuhaler	Discharge channels	AstraZeneca [73]
Twisthaler	Discharge channels	Schering Plough [74]
Pulvinal	Cyclone chamber	Chiesi [75]
Airmax	Cyclone chamber	Ivax Corporation [76]
Novolizer	Cyclone chamber	Viatris [77]
Taifun	Cyclone chamber	LAB International [78]
Ratiopharm Jethaler	Ring compact	Ratiopharm [77]
Ultrahaler	Ring compact	Aventis [70]

drug delivery. As a result of the growing interest in aerosol drug delivery to the lung, the efficiency of delivery has to be optimized. This is achieved by improving the powder formulations with new concepts (**Table 5**). DPI formulations may be micronized drugs mixed with a large particle size excipient, to aid with powder flow, or may consist of drug alone [80]. The size of a drug particle critically influences lung deposition [81], and the nature of the aerosol droplets is dependent on its mass median aerodynamic diameter, which is a function of particle size, shape and density. Aerosols should be neither too large nor too small. Inhaled particles with diameter > 10 µm are deposited in the oropharynx or large airways, where they have few, if any, systemic therapeutic effects [82]. Particles with diameter < 0.5 µm can be inhaled into the deep lung but have a high probability of being exhaled before deposition. The lung can be effectively targeted for COPD treatment by delivering the drug as an aerosol, with an aerodynamic diameter ranging from 1 to 5 µm, and thus most inhaled products are formulated with a high proportion of drug in this size range [83]. To target the alveolar region specifically, the particle diameter of COPD drugs should not be > 3 µm. In addition to particle size, a combination of intrinsic physicochemical properties, shape, surface area and morphology affects the forces of interaction and aerodynamic properties, which in turn determine fluidization, dispersion, delivery to the lung and deposition in the peripheral airways [84]. Thus, strict control of powder properties ensures reproducibility of aerosol deposition and retention within desired regions of the respiratory tract.

In addition to powder technologies, much of the dry powder formulation advancement has been in carrier systems [11], and carrier particles may have a discrete interactive excipient function, or the particle may be a matrix particle that includes active drug dispersed molecularly or homogeneously within its structure [85-87]. Interactive carriers are commonly milled or sieved lactose/sugar alcohol particles

Table 5. Potential dry powder formulations for inhalation therapy.

Formulation type	Details	Ref.
Interactive carrier	Size controlled lactose	
	Pharmatose	[85]
	Inhalac	[86]
	Sugar alcohol	[87]
Modification of carrier surface	Radial spherical crystallization	[52]
	Smooth surface	[89]
Powder engineering	Powderhale	[91]
	PulmoSol particles	[92]
	Large porous particles	[93]
	Pulmosphere particles	[94]
	Solidose particles	[95]
	Tachnosphere particles	[96]
	Promaxx particles	[97]
	Aerodynamically small macroparticles	[93]
	Nanoparticles	[102]
Matrix particle carrier	Chitosan-base carrier	[98]
	PLGA	[105]
Liposome	Conventional liposomes	[100]
	Ligand-appended liposomes	[101]
Absorption enhancer	Surfactant	[52]
	Fatty acid (preferably capric acid)	
	Taurocholate	
Enhanced solubility	Solid dispersion	[115]
	Cyclodextrin	[114]

PLGA: Poly(lactide-*co*-glycolide).

with beneficial aerodynamic characteristics to allow drugs to be carried into an air stream, where they can be dispersed and inhaled [85,86]. Recent alternative strategies include the addition of ternary components to modulate the interaction between drug and carrier particles [88], modification of carrier surface [89] and particle engineering approaches, such as Pulmospheres and Promaxx particles for improved dispersibility and lung deposition [90-97].

4.4.2 Inhalable powder formulations for improved therapeutic outcomes

Matrix particle carrier formulations, with use of chitosan, have received widespread attention, as these technologies were designed for targeted deposition and improved therapeutic outcome [98,99]. In addition, liposomes [100,101], nanoparticles [102] and permeation enhancers [103] have also been believed to be effective tools for improving DPI formulations, to counteract inter-patient variability and barriers to disease treatment. Liposome-based formulations are effective against intracellular pathogens, and their demonstrated advantages include: i) the ability to formulate biologically active molecules; ii) the ability to encapsulate hydrophilic compounds; iii) reduction in the toxicity of active agents; iv) increased therapeutic index; v) increased stability of labile agents; vi) improved pharmacokinetics; vii) increased delivery to target tissues; and viii) the feasibility of nebulization as well as dry powder inhalers [104]. The use of polymeric microparticles to pulmonary administration has also been proposed. Owing to its biodegradability and biocompatibility, poly(lactide-*co*-glycolide) (PLGA) has been a popular choice as a drug carrier [105,106]. By using solvent evaporation as well as spray drying methods, PLGA microparticles encapsulating drugs have been prepared [107], and these techniques resulted in spherical particles with 20 – 30% drug loading and 2.8 – 3.5 μm volume median diameter. Despite the satisfactory results obtained with microparticles, the quest for better drug delivery systems ushered in the era of nanoparticles, and the design and development of polymeric nanoparticles for inhaled therapy have also been attempted [102]. Nanoparticles range in size from 10 to 1000 nm, whereas microparticles lie in the size range 1 – 1000 μm. The difference between microparticles and nanoparticles lies not merely in the size, but also in the ability of nanoparticles to achieve a high drug loading, minimize the consumption of polymers, cross permeability barriers and elicit a better therapeutic response [108,109]. Furthermore, inhaled nanoparticles stand a better chance of mucosal adherence, particle delivery and hence net drug delivery to the lungs [110]. In addition, the use of absorption enhancers, including surfactant, fatty acid (preferably capric acid), taurocholate, saturated polyglycolysed glyceride, trihydroxy bile salt and hyaluronic acid, was also proposed for DPI formulations [52]. These approaches have

been shown to improve the bioavailabilities and pharmacodynamic responses of biotherapeutic agents, as well as new drug entities with low molecular mass [67].

4.4.3 New inhalable powder formulations for poorly soluble drugs

Efficacy of inhaled drugs in the respiratory tract depends on the site of deposition and on the physicochemical properties of the drug, including rate of dissolution and subsequent systemic absorption, metabolism and elimination of the drug. When the drug particles are deposited at the upper airway, mucociliary clearance takes place before dissolution and absorption. The mucociliary clearance rate is generally ~ 1 – 2% per minute with half-life of ~ 1 – 2 h. If the drug particles are deposited at the lower airways, the drug is cleared by macrophages via phagocytosis. The clearance rate by macrophages is significantly slower compared with mucociliary clearance [111]. The inhaled particles of COPD drugs, deposited in the pulmonary region, undergo dissolution in the lung fluids, and the dissolved fraction of the dose is available for absorption across the alveolar membrane [112]. The insoluble particles will probably be engulfed by alveolar macrophages and transported to the mucociliary clearance system, although regional impairment of mucociliary clearance was observed in patients with COPD [113]. Subsequently, drug particles will be carried up to the pharyngeal region where they may be expectorated or swallowed. Thus, COPD drug with poor water solubility and rapid clearance in the lung might show performance limitations, such as incomplete or erratic absorption, poor bioavailability and slow onset of action, possibly resulting in fewer pharmacological activities. In this context, improvement of solubility would be one of the key considerations for clinical application of the poorly soluble drugs as DPI systems.

Cyclodextrins are known to form inclusion complexes with lipophilic drugs as guest molecules and thus improve the solubility of drugs [114]. The enhanced rates of dissolution could lead to improved biological activities of the complexed drugs. Interestingly, cyclodextrins can act as absorption enhancers in the lung, as well. These properties represent advantages in developing COPD drugs for pulmonary delivery. In addition, the authors' group has previously proposed the new solid dispersion of amorphous cyclosporine A (CsA) for inhalation therapy, because of its rapid dissolution behavior [115]. The new DPI system of CsA would meet three major requirements for inhalation therapy of airway inflammation. First, CsA, contained in the DPI system, would dissolve within a reasonable time span, although removal of particles by mucociliary clearance occurs within a couple of hours. Second, the jet-milled solid dispersion of CsA has an aerodynamic size range that is suitable for inhalation. Third, the jet-milled CsA powder shows high emission from the capsule, leading to increased deposition in respiratory systems. The authors' group also demonstrated that the new inhalable powder formulation of CsA could attenuate a marked recruitment of inflammatory cells in the experimental COPD/asthma animal model, without excessive increase in systemic exposure of CsA. On these advantages, a new DPI system of CsA, using solid dispersion techniques, might be a potential medication for the treatment of airway inflammation, and the solid dispersion strategy could be efficacious for other poorly soluble COPD drugs.

5. Expert opinion

The challenges in the development of new therapies for the treatment of COPD include the limited understanding of the molecular pathogenesis of COPD and the lack of integration among new findings on basic researches, the physiological responses and the clinical implications. Despite these issues, several new drug candidates have been proposed and are in clinical development. Many drugs in clinical development might be useful in the treatment of COPD, but few will go beyond the proof-of-concept stage and advance into further clinical development, possibly because of lack of safety and efficacy. According to the current developmental status of COPD drugs, PDE4 inhibitors are likely to be the first candidates to be added to the COPD therapies in the near future. Several anti-inflammatory mechanisms are being investigated clinically in patients with COPD, so further development of COPD drugs might focus on the new strategies to reduce the inflammation and alleviate the clinical symptoms of COPD. Once proof-of-concept has been established for the anti-inflammatory therapies for COPD, the potential for combining with inhaled bronchodilators can be explored with the aim of providing patients with an optimal combination that delivers both symptomatic relief and disease-modifying therapy in a single product. For the accelerated research and development of COPD drugs, it is very important to create the proper experimental COPD model animals and surrogate biomarkers to evaluate the efficacy of new drug entities. Enormous efforts should be made on these tasks, and they could lead to the logical development of new therapeutic strategies for COPD in the future.

Research interest in the route of administration of COPD drugs would lead to breakthroughs in several areas of both formulation and device design, and as such market and benefits to patients might be improved as well. These activities could overcome several limitations and potential problems of inhaled COPD therapy, especially short duration of action and poor stability of agents. The search for more efficient DPI systems would continue to attract substantial research interest among academia and pharmaceutical industries. DPI technology is evolving, with recent devices and formulations being designed to overcome some of perceived limitations of earlier products. Alliances between small technology suppliers and major pharmaceutical companies will also continue to be a cornerstone of product development in future years, hopefully providing stable DPI for COPD drugs with enhanced pulmonary drug delivery, efficacious devices, an easy manufacturing process and high

safety. However, the increasing number of inhaler devices and formulations can be very confusing to patients and caregivers alike, and it can be very frustrating to choose inhaler devices for an individual patient. To ensure the best compliance with therapy, patients need to understand how the devices work and what the drug actually does. In addition, appropriate education from physicians or health-care-givers has a key role in improving inhaler technique and compliance.

Another potential problem on inhalation therapy with COPD drugs is chronic toxicity in the pulmonary tissues. The current status of pulmonary administration of COPD drugs might be promising; however, the possible side effects following chronic use are yet to be ascertained. Further basic and clinical studies on the safety of inhaled COPD drugs would be required in order to avoid serious undesired side effects. In particular, biologics for COPD treatment, such as antibodies against inflammatory mediators and recombinant peptides/proteins, potentially induce some immunological responses, therefore safety assessment on this matter should be essential at an early stage of pharmaceutical development.

In conclusion, better understanding of COPD pathophysiology, such as airway inflammation, oxidative stress and alveolar destruction, has delineated new therapeutic targets, with consequent identification of new compounds with therapeutic potential. As a result of the growing interest in aerosol drug delivery to the airway systems for local effects, together with the new drug candidates for COPD treatment, the efficiency of delivery has to be optimized. This is partly achieved by improving the device performance and powder formulations, and the emerging technologies in this field would be developed to overcome the limitations of the current inhalation therapy for patients with COPD and severe asthma in the future.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet 2004;364:613-20
• **A detailed review on history, prevalence, risk factors and clinical features of COPD.**
2. Halbert RJ, Natoli JL, Gano A, et al. Global burden of COPD: systematic review and meta-analysis. Eur Respir J 2006;28:523-32
3. Anto JM, Vermeire P, Vestbo J, et al. Epidemiology of chronic obstructive pulmonary disease. Eur Respir J 2001;17:982-94
4. Lopez AD, Murray CC. The global burden of disease, 1990-2020. Nat Med 1998;4:1241-3
5. Barnes PJ. Mediators of chronic obstructive pulmonary disease. Pharmacol Rev 2004;56:515-48
6. Fitzgerald MF, Fox JC. Emerging trends in the therapy of COPD: novel anti-inflammatory agents in clinical development. Drug Discov Today 2007;12:479-86
•• **A review on new medications for COPD.**
7. Barnes PJ, Stockley RA. COPD: current therapeutic interventions and future approaches. Eur Respir J 2005;25:1084-106
8. Borgstrom L, Asking L, Thorsson L. Idealhalers or realhalers? A comparison of Diskus and Turbuhaler. Int J Clin Pract 2005;59:1488-95
9. Taylor K. Pulmonary drug delivery, Churchill Livingstone, Edinburgh, 2002
10. Purewal TS. Formulation of metered dose inhalers, Interpharm, Illinois, 1998
11. Smyth HD, Hickey AJ. Carriers in drug powder delivery: implications for inhalation system design. Am J Drug Deliv 2005;3:117-32
12. Churg A, Cosio M, Wright JL. Mechanisms of cigarette smoke-induced COPD: insights from animal models. Am J Physiol Lung Cell Mol Physiol 2008;294:L612-31
13. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 2004;350:2645-53
14. De Boer WI. Cytokines and therapy in COPD: a promising combination? Chest 2002;121:209S-18S
15. Kuwano K. Epithelial cell apoptosis and lung remodeling. Cell Mol Immunol 2007;4:419-29
16. Blease K, Lewis A, Raymon HK. Emerging treatments for asthma. Expert Opin Emerg Drugs 2003;8:71-81
17. Briggs DD. Chronic obstructive pulmonary disease overview: prevalence, pathogenesis, and treatment. J Manag Care Pharm 2004;10:S3-10
18. Jeffery PK. Differences and similarities between chronic obstructive pulmonary disease and asthma. Clin Exp Allergy 1999;29(Suppl 2):14-26
19. Frode TS, Medeiros YS. The puzzle of asthma treatment: animal models to genetic studies. Curr Pharm Des 2005;11:2515-24
20. Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. Lancet 2006;368:780-93
21. Nagai H, Teramachi H, Tuchiya T. Recent advances in the development of anti-allergic drugs. Allergol Int 2006;55:35-42
22. Busse WW, Rosenwasser LJ. Mechanisms of asthma. J Allergy Clin Immunol 2003;111:S799-804
23. Hanania NA, Donohue JF. Pharmacologic interventions in chronic obstructive pulmonary disease: bronchodilators. Proc Am Thorac Soc 2007;4:526-34
24. Tashkin DP, Pearle J, Iezzoni D, et al. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. COPD 2009;6:17-25
25. Gross NJ, Co E, Skorodin MS. Cholinergic bronchomotor tone in COPD. Estimates of its amount in comparison with that in normal subjects. Chest 1989;96:984-7
26. Vincken W, van Noord JA, Greefhorst AP et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Eur Respir J 2002;19:209-16
27. Barnes PJ. Theophylline for COPD. Thorax 2006;61:742-4
28. Johnson M. Corticosteroids: potential beta2-agonist and anticholinergic

interactions in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2:320-5; discussion 40-1

29. Caramori G, Adcock I. Pharmacology of airway inflammation in asthma and COPD. Pulm Pharmacol Ther 2003;16:247-77
30. Barnes PJ. Corticosteroid resistance in airway disease. Proc Am Thorac Soc 2004;1:264-8
31. Cazzola M, Matera MG, Lotvall J. Ultra long-acting beta 2-agonists in development for asthma and chronic obstructive pulmonary disease. Expert Opin Investig Drugs 2005;14:775-83
32. Fitzgerald MF, Fox JC. Emerging trends in the therapy of COPD: bronchodilators as mono- and combination therapies. Drug Discov Today 2007;12:472-8
33. Matera MG, Cazzola M. Ultra-long-acting beta2-adrenoceptor agonists: an emerging therapeutic option for asthma and COPD? Drugs 2007;67:503-15
34. Onoue S, Yamada S, Yajima T. Bioactive analogues and drug delivery systems of vasoactive intestinal peptide (VIP) for the treatment of asthma/COPD. Peptides 2007;28:1640-50
35. Said SI. Vasoactive intestinal polypeptide and asthma [editorial]. N Engl J Med 1989;320:1271-3
36. Donnelly LE, Rogers DF. Therapy for chronic obstructive pulmonary disease in the 21st century. Drugs 2003;63:1973-98

• **A review on new therapeutic strategies of COPD treatment.**

37. Gueders MM, Foidart JM, Noel A, et al. Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs in the respiratory tract: potential implications in asthma and other lung diseases. Eur J Pharmacol 2006;533:133-44
38. Hu J, Van den Steen PE, Sang QX, et al. Matrix metalloproteinase inhibitors as therapy for inflammatory and vascular diseases. Nat Rev Drug Discov 2007;6:480-98
39. Barnes PJ. New treatments for COPD. Nat Rev Drug Discov 2002;1:437-46
40. Barnes PJ. Emerging pharmacotherapies for COPD. Chest 2008;134:1278-86

•• **A detailed review on current and new medications for COPD.**

41. Rennard SI. Antiinflammatory therapies other than corticosteroids. Proc Am Thorac Soc 2004;1:282-7
42. Cheng J, Grande JP. Cyclic nucleotide phosphodiesterase (PDE) inhibitors: novel therapeutic agents for progressive renal disease. Exp Biol Med (Maywood) 2007;232:38-51
43. Spina D. PDE4 inhibitors: current status. Br J Pharmacol 2008;155:308-15

• **A detailed review on the current status of PDE4 inhibitors for the treatment of asthma and COPD.**

44. Hasko G, Linden J, Cronstein B, et al. Adenosine receptors: therapeutic aspects for inflammatory and immune diseases. Nat Rev Drug Discov 2008;7:759-70
45. Stockley RA. Neutrophils and the pathogenesis of COPD. Chest 2002;121:151S-5S
46. Adcock IM, Chung KF, Caramori G, et al. Kinase inhibitors and airway inflammation. Eur J Pharmacol 2006;533:118-32
47. Gonsiorek W, Fan X, Hesk D, et al. Pharmacological characterization of Sch527123, a potent allosteric CXCR1/CXCR2 antagonist. J Pharmacol Exp Ther 2007;322:477-85
48. Dugo L, Marzocco S, Mazzon E, et al. Effects of GW274150, a novel and selective inhibitor of iNOS activity, in acute lung inflammation. Br J Pharmacol 2004;141:979-87
49. Hansel TT, Kharitonov SA, Donnelly LE, et al. A selective inhibitor of inducible nitric oxide synthase inhibits exhaled breath nitric oxide in healthy volunteers and asthmatics. FASEB J 2003;17:1298-300
50. Barnes PJ. Cytokine modulators as novel therapies for airway disease. Eur Respir J 2001;18:67s-77s
51. Newman SP. Dry powder inhalers for optimal drug delivery. Expert Opin Biol Ther 2004;4:23-33

•• **A review on the development of DPI device and formulation technology.**

52. Onoue S, Hashimoto N, Yamada S. Dry powder inhalation systems for pulmonary delivery of therapeutic peptides and proteins. Expert Opin Ther Patents 2008;18:429-42
53. van der Palen J, Klein JJ, van Herwaarden CL et al. Multiple inhalers confuse asthma patients. Eur Respir J 1999;14:1034-7
54. Rau JL. Practical problems with aerosol therapy in COPD. Respir Care 2006;51:158-72

• **A detailed review on problems of inhalation systems.**

55. Corden ZM, Bosley CM, Rees PJ, et al. Home nebulized therapy for patients with COPD: patient compliance with treatment and its relation to quality of life. Chest 1997;112:1278-82
56. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. Respir Care 2005;50:1360-74; discussion 74-5
57. Geller DE. Comparing clinical features of the nebulizer, metered-dose inhaler, and dry powder inhaler. Respir Care 2005;50:1313-21; discussion 21-2
58. Pickering H, Pitcairn GR, Hirst PH, et al. Regional lung deposition of a technetium 99m-labeled formulation of mometasone furoate administered by hydrofluoroalkane 227 metered-dose inhaler. Clin Ther 2000;22:1483-93
59. Kohler D. Novolizer: the new technology for the management of asthma therapy. Curr Opin Pulm Med 2003;9(Suppl 1):S11-6
60. Atkins PJ. Dry powder inhalers: an overview. Respir Care 2005;50:1304-12; discussion 12
61. Dhand R. Inhalation therapy with metered-dose inhalers and dry powder inhalers in mechanically ventilated patients. Respir Care 2005;50:1331-4; discussion 44-5
62. Newman SP. Therapeutic aerosols, Butterworths, London, 1984
63. Bell JH, Hartley PS, Cox JS. Dry powder aerosols. I. A new powder inhalation device. J Pharm Sci 1971;60:1559-64
64. Dahl R, Backer V, Ollgaard B, et al. Assessment of patient performance of the HandiHaler compared with the metered dose inhaler four weeks after instruction. Respir Med 2003;97:1126-33
65. Frijlink HW, De Boer AH. Dry powder inhalers for pulmonary drug delivery. Expert Opin Drug Deliv 2004;1:67-86

• **A review on concepts, devices and formulations of DPI.**

66. Ikegami K, Kawashima Y, Takeuchi H, et al. Improved inhalation behavior of steroid KSR-592 in vitro with Jethaler by polymorphic transformation to needle-like crystals (beta-form). Pharm Res 2002;19:1439-45

67. Agu RU, Ugwoke MI, Armand M, et al. The lung as a route for systemic delivery of therapeutic proteins and peptides. Respir Res 2001;2:198-209
68. Pover GM, Langdon CG, Jones SR, et al. Evaluation of a breath operated powder inhaler. J Int Med Res 1988;16:201-3
69. Villax P, Brito V, Steckel H. Development and performance of a new simple dry powder inhaler operating at low airflow eates, Davis Horwood International, Raleigh, NC, 2002
70. Han R, Papadopoulos G, Greenspan B. Investigation of powder dispersion inside a SPIROS dry powder inhaler using particle image velocimetry. Powd Technol 2002;125:266-78
71. Parry-Billings M, Boyes R, Clisby L, et al. Design, development and performance of a multidose dry powder inhaler. Pharm Technol 2000;12:38-45
72. Dahl R, Creemers JP, Van Noord J, et al. Comparable efficacy and tolerability of formoterol (Foradil) administered via a novel multi-dose dry powder inhaler (Certihaler) or the Aerolizer dry powder inhaler in patients with persistent asthma. Respiration 2004;71:126-33
73. Wetterlin K. Turbuhaler: a new powder inhaler for administration of drugs to the airways. Pharm Res 1988;5:506-8
74. Fan B, Yang T, Keaton D. Application of computer modeling in the design and development of the new mometasone furoate dry powder inhaler (F-dpi) nozzle. Serentec Press, Raleigh, 2000
75. Meakin BJ, Ganderton D, Panza I, et al. The effect of flow rate on drug delivery from the Pulvinal, a high-resistance dry powder inhaler. J Aerosol Med 1998;11:143-52
76. Keating GM, Faulds D. Airmax: a multi-dose dry powder inhaler. Drugs 2002;62:1887-95; discussion 96-7
77. de Boer AH, Gjaltema D, Hagedoorn P, et al. Comparative in vitro performance evaluation of the Novopulmon 200 Novolizer and Budesonid-ratiopharm Jethaler: two novel budesonide dry powder inhalers. Pharmazie 2004;59:692-9
78. Seppala OR, Aalto E, Annila I, et al. The efficacy of a new salbutamol metered-dose powder inhaler in comparison with two other inhaler devices. Respir Med 2001;95:949-53
79. Rau JL. The inhalation of drugs: advantages and problems. Respir Care 2005;50:367-82
80. Byron PR. Aerosol formulation, generation, and delivery using non-metered and metered systems, CRC Press, Inc., Boca Raton, FL, 1990
81. Suarez S, Hickey AJ. Drug properties affecting aerosol behavior. Respir Care 2000;45:652-66
82. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: physiological factors affecting therapeutic effectiveness of aerosolized medications. Br J Clin Pharmacol 2003;56:588-99
• **A review on physiological factors affecting therapeutic effectiveness of inhaled drug therapy.**
83. Chrystyn H. Is total particle dose more important than particle distribution? Respir Med 1997;91:(Suppl A):17-9
84. Telko MJ, Hickey AJ. Dry powder inhaler formulation. Respir Care 2005;50:1209-27
• **A detailed review on the development of DPI formulations and characterization strategies.**
85. Thibert R, Parry-Billings M, Shott M. Clickhaler dry powder inhaler: focussed in vitro proof of principle evaluation of a new chemical entity for asthma. Int J Pharm 2002;239:149-56
86. de Boer AH, Hagedoorn P, Gjaltema D, et al. Air classifier technology (ACT) in dry powder inhalation Part 4. Performance of air classifier technology in the Novolizer multi-dose dry powder inhaler. Int J Pharm 2006;310:81-9
87. Endo K, Amikawa S, Matsumoto A, et al. Erythritol-based dry powder of glucagon for pulmonary administration. Int J Pharm 2005;290:63-71
88. Louey MD, Stewart PJ. Particle interactions involved in aerosol dispersion of ternary interactive mixtures. Pharm Res 2002;19:1524-31
89. Larhrib H, Martin GP, Marriott C, et al. The influence of carrier and drug morphology on drug delivery from dry powder formulations. Int J Pharm 2003;257:283-96
90. Chan HK, Clark A, Gonda I, et al. Spray dried powders and powder blends of recombinant human deoxyribonuclease (rhDNase) for aerosol delivery. Pharm Res 1997;14:431-7
91. Staniforth JN. Pre-formulation aspects of dry powder aerosols, Interpharm Press, Buffalo Grove, 1996
92. Patton JS. Deep-lung delivery of therapeutic proteins. Chemtech 1997;27:34-8
93. Edwards DA, Hanes J, Caponetti G, et al. Large porous particles for pulmonary drug delivery. Science 1997;276:1868-71
94. Bot AI, Tarara TE, Smith DJ, et al. Novel lipid-based hollow-porous microparticles as a platform for immunoglobulin delivery to the respiratory tract. Pharm Res 2000;17:275-83
95. Blair J, Mao L, Hodgers E. Modification of the pulmonary absorption of cyclosporin using SoliDose technology, Serentec Press, Raleigh, 2000
96. Wilson BR, Grant MI, Steiner SS, et al. Technospheres for pulmonary and nasal applications, Davis Horwood, Raleigh, 2002
97. Mandal TK. Inhaled insulin for diabetes mellitus. Am J Health Syst Pharm 2005;62:1359-64
98. Li HY, Birchall J. Chitosan-modified dry powder formulations for pulmonary gene delivery. Pharm Res 2006;23:941-50
99. Shahiwala A, Misra A. A preliminary pharmacokinetic study of liposomal leuprolide dry powder inhaler: a technical note. AAPS PharmSciTech 2005;6:E482-6
100. Pandey R, Sharma S, Khuller GK. Nebulization of liposome encapsulated antitubercular drugs in guinea pigs. Int J Antimicrob Agents 2004;24:93-4
101. Vyas SP, Kannan ME, Jain S, et al. Design of liposomal aerosols for improved delivery of rifampicin to alveolar macrophages. Int J Pharm 2004;269:37-49
102. Ostrander KD, Hovey DC, Knapp DA, et al. Potential delivery of advantages of spray-dried nanocrystal colloidal budesonide with Clickhaler, Serentec Press, Raleigh, 2000
103. Wollmer P, Backstrom K, Zhao H, et al. Surface active agents as enhancers of alveolar absorption. Pharm Res 2000;17:38-41
104. Khuller GK, Kapur M, Sharma S. Liposome technology for drug delivery against mycobacterial infections. Curr Pharm Des 2004;10:3263-74
105. Sivadas N, O'Rourke D, Tobin A, et al. A comparative study of a range of polymeric microspheres as potential carriers

for the inhalation of proteins. Int J Pharm 2008;358:159-67

106. Jain RA. The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices. Biomaterials 2000;21:2475-90
107. O'Hara P, Hickey AJ. Respirable PLGA microspheres containing rifampicin for the treatment of tuberculosis: manufacture and characterization. Pharm Res 2000;17:955-61
108. Pandey R, Khuller GK. Polymer based drug delivery systems for mycobacterial infections. Curr Drug Deliv 2004;1:195-201
109. Rao GC, Kumar MS, Mathivanan N, et al. Nanosuspensions as the most promising approach in nanoparticulate drug delivery systems. Pharmazie 2004;59:5-9
110. Jacobs C, Muller RH. Production and characterization of a budesonide nanosuspension for pulmonary administration. Pharm Res 2002;19:189-94
111. Daviskas E, Anderson SD, Gonda I, et al. Changes in mucociliary clearance during and after isocapnic hyperventilation in asthmatic and healthy subjects. Eur Respir J 1995;8:742-51
112. Dolovich MB, Jordana M, Newhouse MT. Methodologic considerations in mucociliary clearance and lung epithelial absorption measurements. Eur J Nucl Med 1987;13(Suppl):S45-52
113. Smaldone GC, Foster WM, O'Riordan TG, et al. Regional impairment of mucociliary clearance in chronic obstructive pulmonary disease. Chest 1993;103:1390-6
114. Matilainen L, Jarvinen K, Toropainen T, et al. In vitro evaluation of the effect of cyclodextrin complexation on pulmonary deposition of a peptide, cyclosporin A. Int J Pharm 2006;318:41-8
115. Onoue S, Sato H, Kawabata Y, et al. In vitro and in vivo characterization on amorphous solid dispersion of cyclosporine A for inhalation therapy. J Control Release. In press

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