CHAPTER

5 Particle-manufacturing technology-based inhalation therapy for pulmonary diseases

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5.1 INTRODUCTION

Lung tissue plays an essential role in the acquisition of oxygen and emission of carbon dioxide. As lung disorders causing breathlessness may be linked with life-threatening matters such as an asthma attack, inhalation therapy using vapourised alkaloids has been performed since the period of ancient Egypt ca. sixteenth century BC [1]. Recent technologies are capable of generating inhalable aerosols from liquids including suspension and solid dry powders, which aerosols are one of the efficient ways of taking medicines.

Human lungs have a wide surface area of approx. 100 m^2, which is second only to that of the intestinal tract, and a vascular network in the alveoli, where gas-exchange occurs [2]. The distal part of lung tissue is composed of thin membranes with a thickness of 0.1–0.2 μm formed by elongated type I epithelial cells, whose membranes enable gas-permeation [3]. Taking into account the above-mentioned facts, the lungs would be expected to be a better drug-absorption site than other mucosal tissues. In addition, the absorption of active agents from the lungs has the advantage of circumventing first-pass metabolism in the liver that would occur in the case of absorption from intestinal tissue.

In this chapter, pulmonary diseases requiring essential medical treatment and promising formulations for treatment of those diseases through inhalation will be described along with current clinical and experimental issues. Also, pulmonary defence systems affecting the activity of inhaled agents will be reviewed.

5.2 PULMONARY DISEASES

5.2.1 PULMONARY TUBERCULOSIS

Pulmonary tuberculosis (TB) is still considered to be an intractable disease like acquired immunodeficiency syndrome and malaria. From a report by the World Health Organization (WHO), 8.7 million people around the world fell ill with TB, and 1.4 million of them died from it in 2011 [4]. Another survey by the WHO estimated that one-third of the world population has already been infected with tubercle bacilli [5, 6]. The establishment of an effective treatment for pulmonary TB is thus still a major public health challenge.

Current treatment for TB is performed by an internationally accepted first-line treatment regimen using isoniazid (INH), rifampicin (RFP), pyrazinamide and ethambutol. However, continuous dosing for more than 6 months is necessary to overcome TB by the standard therapy protocol. In addition, owing to this long-lasting treatment, the eradication of the tubercle pathogen often fails because of the emergence of multidrug-resistant TB, which is a major issue. The WHO carries out a drug adherence strategy called directly observed therapy, short course, and it has been successful in bringing about certain beneficial results [7].

The tubercle pathogen, *Mycobacterium tuberculosis*, infects alveolar macrophage cells and persists in the macrophage by preventing phago-lysosomal fusion [8–10]. In addition, *M. tuberculosis* is naturally resistant to the macrophage oxidative

burst that occurs via NADPH oxidase due to the generation of catalase and peroxidase [11, 12]. To combat the pathogen, the infected macrophage cells exhibit inflammatory responses that lead to recruitment of mononuclear cells from neighbouring blood vessels. These mononuclear cells differentiate into multinucleate giant cells and epithelioid cells that cooperate with lymphocytes to isolate the pathogen by surrounding *M. tuberculosis*-bearing cells and eventually to form a granuloma, a characteristic pathology of TB [13–15]. However, *M. tuberculosis*, in turn, exploits the granuloma as a shelter to escape from monitoring by immune cells and attack by antibiotics. Hence, direct delivery of antitubercular agents into the granuloma would be a promising approach for effective treatment of TB in a short period.

5.2.2 LUNG CANCER

Lung cancer is divided into two types, small cell lung cancer and non-small cell lung cancer (NSCLC), based on the differences in pathological tissues; and these cancers are the leading cause of death among malignant neoplasms [16, 17]. Current treatment for lung cancer is performed by surgery, radiotherapy, chemotherapy and their combinations. Among them, chemotherapy is generally performed due to its effectiveness to suppress the development of additional lung cancer cells. However, resistance to chemotherapeutic agents is frequently observed in NSCLC patients, causing clinical problems; because the 5-year survival rate of NSCLC patients is $<15\%$ [18, 19]. In addition, another widely known problem with cancer therapy using chemotherapeutic agents is that such agents have various side effects such as pancytopenia and multi organ failure owing to bone-marrow depression [18]. To overcome these problems, local administration of anticancer agents would be expected to be effective for the treatment of lung cancer without systematic side effects.

A first attempt at selective delivery of anticancer agents to cancer cells is based on the enhanced permeation and retention (EPR) effect, by which nanoparticles having a diameter of around 100–200 nm passively accumulate in tumour foci [20]. SMANCS, a conjugate of neocarzinostatin and poly(styrene-*co*-maleic acid), has been commonly used for the treatment of hepatic cancer as a treatment based on this EPR effect. However, selective accumulation of intravenously injected nanoparticles in a specific target tissue, such as the lungs, is still a challenging issue. To address this challenge, the surface of nanoparticles can be conjugated with polyethylene glycol to allow these particles to escape from recognition and entrapment by the reticuloendothelial system in the liver and to increase the number of them that reach the desired target [21]. In the case of lung cancers, inhalation of anticancer agents is another possible way to achieve their selective delivery to the lungs and effective treatment.

5.2.3 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is characterised by the progressive development of airflow limitation that is not fully reversible [22]. The airflow obstruction is usually progressive and associated with a chronic inflammation caused

by tobacco smoking and noxious particles/gases derived from the burning of wood and other biomass fuels [23, 24]. The global prevalence of COPD has reached epidemic proportions; and this disease was the fourth leading cause of death worldwide in 2008 [25, 26].

The most common symptoms of COPD patients are cough, high sputum production and dyspnea. COPD is diagnosed by the presence of symptoms and assessment of airway obstruction in addition to historical exposure to risk factors such as tobacco smoke. The airway obstruction is assessed by determination of forced expiration volume in 1 s (FEV1) and forced vital capacity (FVC) after administration of a bronchodilator [24]. A ratio of these two parameters, FEV1/FVC, of <0.7 means the presence of airflow limitation.

Treatment for COPD presently employed is similar to that for asthma, as it involves the application of bronchodilators such as β2-agonists along with anti-inflammatory corticosteroids. However, these treatments do not lead to recovery from the pathological state but just prevent disease progression. In addition, the inhalation of therapeutic agents in patients with COPD is limited, owing to their decreased inspiratory capacity.

5.3 LUNG DEFENCE SYSTEM

5.3.1 STRUCTURE

All animals naturally breathe to bring oxygen into and to eliminate carbon dioxide from the blood passing through their lungs, the breath frequency being over 20,000 times per day in adult humans. In such a huge number of breaths, the lung tissue has intriguing defence systems to prevent the invasion of foreign substances such as pathogens and toxic artefacts.

Air is conducted to the distal lung structures, namely, the alveoli, through 23 bifurcations of the airway starting from the mouth or nose in humans [27]. As shown in Figure 5.1, the airway consists of a conducting zone and a respiratory zone. The conducting zone begins at the mouth or nose and comprises the trachea, bronchi and bronchioles, with approx. 19 steps of bifurcation of the bilateral airways. Then, the respiratory zone is reached, consisting of alveolar ducts, which bifurcate several times, and the terminal alveolar sacs. The surface area of the lungs is estimated to be approx. 100 m^2, which is almost half of that of the intestines, being approx. 250 m^2 [28]. Hence, the lung tissue is also expected to be useful as a drug-absorption site for systemic actions.

The airways become narrower with each bifurcation; in humans, a diameter of 1.8 cm at the beginning of the airways decreases to one of 0.041 cm at the distal airway where gas-exchange takes place [27]. This lung structure means that there is a size limitation for particles to reach the distal absorption site. At an airway branching site, air flow collides with the airway wall due to inertial impact, with the consequence being turbulence flow. As a result, inhaled particles would be trapped in

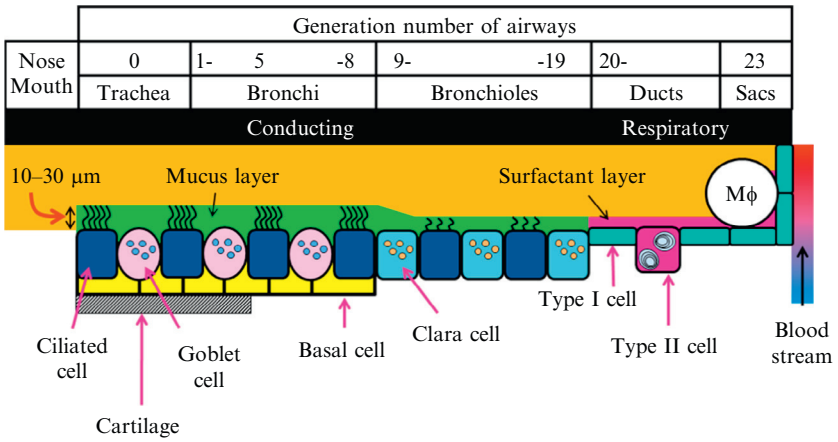

FIGURE 5.1

Structure of the lung defense system.

the airways without reaching the alveoli. The manufacture of particles that move in the air flow and have a favourable size to be delivered to the alveoli is important to attain effective inhalation treatment for pulmonary diseases.

5.3.2 MUCUS LAYER

When particles accidentally invade into the lung tissue, they are eliminated by mucus production and mucociliary movement. As shown in Figure 5.1, mucus-producing cells such as goblet cells and Clara cells are interspersed in the airway walls in the conducting zone and generate mucus by an interaction with the nervous system as soon as the particles are recognised by those cells [29]. Mucus that has trapped the particles is transported by ciliated cells by way of ciliary motion that sweeps the mucus upwards. These serial eliminating reactions are called mucociliary clearance or mucociliary escalator, and they play a role in the defence system in the upper airways.

The major component of mucus is a glycoprotein called mucin, the molecular weight of which ranges from 500 to 40,000 kDa. The shape of a single molecule of mucin having a diameter of 3–10 nm and a length of 100–500 nm is fibrelike, and mucin molecules stack to form an assembly having a three-dimensional meshwork with a 5–10 μm thickness [30]. This mucin meshwork, known as fibrous mucin, has an interesting structure comprising mucins having many pores of several microns in diameter; furthermore, there is another meshwork with pores of approximately 500 nm in its fibrous structure [31]. Namely, the mucus meshwork is able to cope with invaders having various sizes, ranging from nanometres for viruses to micrometres for bacteria, by these two different pore sizes.

5.3.3 PULMONARY SURFACTANT

In the respiratory zone, pulmonary surfactant is generated by type II epithelial cells and forms a liquid layer with a thickness of 0.1–0.9 μm that covers the airway walls to help maintain the alveolar structure during the stretching and shrinking of the terminal airways that occurs during breathing [32]. According to the lung model established by Weibel [27], the surface area integrated from the 20th branching sites to the alveoli is 78.3×10^4 cm^2. Thus, the volume of the surfactant covering the surface of the respiratory zone is calculated to be approximately 8–70 mL. Hence, the lungs are less favourable for the dissolution of dry powders due to the low amount of the liquid surfactant present in them than the gastrointestinal tract, where several litres of digestive liquids are secreted every day.

Secreted pulmonary surfactant is mostly recycled by the type II epithelial cells themselves, but the half-life of the surfactant is estimated at 6–7 h because of uptake of it by alveolar macrophage cells and dendritic cells [33]. The surfactant contains various proteins such as surfactant proteins (SPs) -A, -B, -C and -D. Among them, the hydrophilic proteins SP-A and SP-D are associated with active uptake by the phagocytic cells and play a role in the innate defence system eliminating foreign substances [34–36]. Whereas, the hydrophobic proteins SP-B and SP-C contribute to the operation of the surfactant recycling system with modification of surface tension by forming a stable surfactant monolayer [37, 38]. In addition, SP-B and SP-C show an adjuvant effect in response to influenza virus antigens by promoting the delivery of the antigens into the nasal antigen-presenting cells [39]. Thus, the interaction of inhaled particles with pulmonary surfactant components is important for the efficient deposition and selective delivery of these particles into the lung cells.

5.4 CHARACTERISTICS OF INHALABLE PARTICLES

5.4.1 PARTICLE SIZE

As the airways become narrower with the development of bifurcations, there is a size limitation to the delivery of particles to the distal absorption sites, the alveolar sacs. Particle size in the airflow is different from its geometric size due to the emergence of drag force dependent on the velocity and is defined as the aerodynamic diameter, which helps to estimate how particles will be deposited in the respiratory system. The aerodynamic diameter D_{aer} is given below:

$$D_{\mathrm{aer}} = D_{\mathrm{geo}} \times \sqrt{\frac{\rho}{\chi}}$$

where D_{geo} is the geometric diameter, ρ is the particle density, χ is the shape factor (a sphere gives 1, but elongated particles such as fibres and needles are >1) [40]. From the mathematical model based on the experimental data, particles with a D_{aer} between 1 and 5 μm are estimated to be efficiently deposited in the alveolar pulmonary region [41]. Almost all large particles of $D_{\mathrm{aer}} > 10$ μm are trapped at the

oropharynx; whereas small particles of $D_{aer} < 1$ μm reach the alveoli, but most of them are exhaled without settlement there [41, 42].

5.4.2 DISPERSIBILITY

Dry-powder particles in bulk form aggregates by cohesive interactions between the particles that arise from various factors such as electrostatic effect, moisture absorption and van der Waals forces [43]. Dispersibility of the dry-powder particles is a key factor giving reproducible splitting into monodispersed particles for optimal deposition in the distal lung tissues. Modification of size, shape and surface roughness of dry-powder particles is effective to reduce particle cohesiveness. For instance, large porous particles with a D_{aer} favourable for inhalation show a considerable deposition in the lungs [44], basically because large particles form fewer aggregates than small particles. The number of contact points between particles per unit volume is smaller for larger particles, thus decreasing the particle aggregation due to a reduction in van der Waals forces [44]. In addition, it is noteworthy that the aerodynamic size of the large porous particles is considerably smaller than their geometric size due to the porosity, which contributes to the decrease in the particle mass density (ρ) [45, 46]. Thus, the large porous particles are favourable for inhalable formulations.

Similarly, an elongated or rough shape decreases cohesive force due to a reduction in their contact points [47]. Lactose, which is usually used as a carrier for inhalation of dry particles, has a rough surface with submicron-sized dimples in which the inhalation drugs become stuck [48]. The van der Waals forces between lactose and inhalation drugs become weaker due to a decrease in contact points caused by the surface roughness. As a result, the inertial forces in the air stream applied to the inhaled particles results in separation of the stuck drugs from the lactose dimples.

5.5 MANUFACTURING TECHNOLOGIES FOR PRODUCTION OF INHALABLE PARTICLES

5.5.1 MILLING

Deposition of inhalation particles on the alveolar surface in the respiratory tract is achieved well by particles with an aerodynamic diameter of between 1 and 5 μm. Technology that generates particles having a wide range of particle sizes from various materials is required for inhalation therapy. Milling is the mechanical process of reducing particle size. Milling technologies such as jet milling and ball milling can produce particles of <5 μm in diameter by the generation of various forces derived from pressurisation, fractioning, shearing and impaction. The majority of currently marketed inhalation medicines such as metered-dose inhalants, nebulized suspensions and dry-powder particles are manufactured based on milling [49]. It should be taken into account that the milling process may affect the stability of heat-labile biological compounds, such as proteins and peptides, owing to increase in local

temperature [50]. Hence, milling of peptides is performed by suspending them in an ice-cold fluid propellant with a pearl-mill equipped with a cryostat to avoid loss of their biological activity [51, 52].

5.5.2 SPRAY-DRYING

Spray-drying is one of the most common technologies to manufacture inhalable dry particles in a large-scale production. Manufacturing dry particles by the spray-drying method proceeds in such a way that active pharmaceutical ingredients (APIs) and excipients, if any, are dissolved in aqueous or organic solvents, after which the solution thus obtained is sprayed through a narrow atomization nozzle with high pressurised air at a temperature higher than the vapourisation point of the solvent. The fine droplets thus emitted are quickly dried, followed by collection of particles generated by a cyclone mechanism. The particle size is regulated by the concentration of API or excipients in the solution and the pressure given to the air flow. There are various types of nozzles used for spray-drying, such as rotary atomizers, pressure nozzles, two-fluid nozzles, four-fluid nozzles with in-line mixing and ultrasonic atomizers [53, 54].

Typically, the drying air temperature is considerably higher than the vapourisation point of the solvent; but the actual temperature subjected to the emitted droplets is lower than the drying air temperature due to the heat of vapourisation. Indeed, heat-labile insulin was successfully formulated into microparticles by the spray-drying method as the first inhaled insulin product, known as Exubera [55]. However, particles subjected to the spray-drying process become amorphous due to a quick phase transition [56]. Prevention of exposure to humidity is necessary to exhibit reproducible dispersion of the spray-dried products.

5.5.3 ENCAPSULATION BY LIPIDS

Lipid is one of the major components of organisms, playing an essential role in the barrier between the cell and its surroundings by forming a lipid-bilayer cell membrane. Major components of the cell membrane include various phospholipids having a phosphatidyl moiety backbone with an alcoholic residue such as choline, ethanolamine or glycerol and two alkyl chain residues such as lauroyl, palmitoyl or stearoyl [57]. Cholesterol also contributes to the robust structure of the biomembrane. Particles formed from these lipids in an aqueous environment form a lipid bilayer representing a w/o/w emulsion and are called liposomes, structures that are able to enclose a hydrophilic drug in their aqueous interior and a hydrophobic drug in their lipid bilayer. In addition, the liposome is regarded to be biocompatible, because its component lipids are derived from natural cell membranes.

Liposomes are prepared by various technologies based on mixing, sonication and pressurisation. Taking for an example the Bangham method [58, 59], lipids are homogeneously dissolved in an organic solvent such as chloroform and then the solvent is evaporated to form a thin film of lipids. An aqueous solution usually

containing an API is subsequently mixed with the lipid film, and then mechanically the mixture is mixed vigorously or sonicated. As a result, liposomes containing an API in their aqueous interior are developed. However, the efficiency of trapping API in liposomes prepared by Bangham's method is not high, being only up to approximately 40%. To improve this low trapping efficiency, other technologies such as the remote loading method, based on a pH-gradient that yields a high encapsulation rate of approximately 100%, have been developed [60, 61].

5.5.4 FREEZE-DRYING

The technology of freeze-drying is widely applied to various fields including medicine. The freeze-drying process proceeds *via* three steps, namely, freezing, primary drying due to a vacuum and secondary drying due to elevated temperature. Freeze-drying of materials frequently makes the materials become amorphous, and thus these products must be protected from humidity.

Spray freeze-drying is one of the technologies exploiting the freeze-drying technique and is basically similar to the spray-drying technology except that the spraying process is performed by using a cryogenic liquid such as liquid nitrogen and the drying is performed under ambient temperature [62, 63]. Particulate products manufactured by spray freeze-drying show lighter and more porous particles than those prepared by the spray-drying method. Spray freeze-drying efficiently produces particles in a high yield of almost 100%, and it is favourable to formulate heat-labile agents into inhalable forms without a decrease in activity.

Freeze-drying technology brings interesting formulations, as exemplified by the Otsuka dry-powder inhalation system [64]. An agglomerated form like a cake is able to be prepared by the freeze-drying method, and the formulation is dispersed into inhalable particles of appropriate size by breath impaction. Namely, the generation of particles and inhalation of them are simultaneously achieved by this system. In addition, lung deposition based on this system is unaffected by a flow rate of inhalation between 20 and 40 L/min [65].

5.6 CLINICAL APPLICATIONS OF INHALABLE PARTICLES

5.6.1 PULMONARY TUBERCULOSIS THERAPY

Spray-drying technology is widely utilised to formulate various APIs into microparticles. Various antitubercular agents such as RFP and capreomycin are spray-dried with poly(lactic-*co*-glycolic) acid (PLGA) as a base for inhalation therapy [66, 67], because tuberculosis mainly develops in the lung. The RFP–PLGA microparticles show a high potential to carry the RFP into phagocytic macrophage cells, where the tubercle pathogen resides; and the amount of RFP detected in the macrophage cells is 10–20 times greater than that of RFP administered in a solution form [68, 69]. The formulation of an API into microparticles significantly improves its uptake by macrophages, because macrophages tend to phagocytose microparticles more

efficiently by uptake through passive diffusion. In addition, RFP–PLGA microparticles exert a potent antitubercular activity towards mycobacteria that have infected alveolar macrophage cells *in vitro*, the effect being 10 times greater than that seen with RFP administered in a solution form [69].

Other attempts regarding encapsulation of hydrophilic antituberculosis agents, such as INH and aminoglycoside, into microspheres are progressing. These antituberculosis agents are entrapped into PLGA microspheres by various methods, such as double-emulsification and spray-drying [70, 71]. As hydrophilic agents are incapable of penetrating the cell membrane, the delivery of such agents by exploiting phagocytic uptake by macrophage cells beneficially increases the intracellular deposition of the agents. In addition, the spray-drying technology is able to provide microparticles containing either hydrophilic or hydrophobic agents or both [72, 73]. The integration of various antitubercular agents is preferable for the treatment of tuberculosis, which requires multiple antituberculosis agents to prevent the emergence of drug-resistant *M. tuberculosis*.

In small animals, RFP–PLGA microparticles do not seem to show significant antitubercular activity as compared to the activity achieved by the conventional per os administration [74, 75], although pulmonary administration of these microparticles leads to a greater, but transient, deposition of RFP in the lungs than per os administration [76]. The reason for this difference is not clear at present, and a better understanding of the mechanism of the pulmonary clearance system and of the interaction of inhaled particles with *M. tuberculosis* and alveolar macrophages will be needed to explain it.

5.6.2 NANOPARTICLE-BASED LUNG CANCER THERAPY

Nano-sized particles can reach the distal lung alveoli, after which, however, they are exhaled without being trapped in them due to their gas-like behaviour in the air flow. The formulation of nanoparticles into aggregates with appropriate excipients, termed nano-composite particles, which have a diameter favourable for inhalation, was studied in an attempt to achieve efficient deposition of nanoparticles in the lungs [77, 78]. However, redispersion of the nano-composite particles into their component parts is necessary to exploit the advantage of the nanoparticles, such as transition into epithelial cells and the bloodstream. For attaining this, water-soluble excipients, such as mannitol and trehalose, are employed to prepare the nano-composite particles; because their use is favourable for inhibition of aggregation of the nanoparticles in the composite microparticles. Nano-composite particles are manufactured by spray-drying technology: nanoparticles are homogeneously suspended in aqueous solvents containing lactose or trehalose, and then spray-dried to be assembled as microparticles.

Nano-sized particles are expected to be efficient for the delivery of antitumour agents into tumour cells. These particles are regarded to be taken up by endocytic pathways, even in epithelial cells. TAS-103, an antitumour agent having a suppressive potential towards topoisomerase I/II, was formulated into nano-composite

particles for the treatment of lung cancer [78]. The composite particles having a diameter of 3 μm and assembled with sugar excipients are redispersed into nanoparticles 200 nm in diameter as soon as they encounter an aqueous solution. As the endocytic pathway in cancer cells is active in ingesting small particles with a diameter of <1 μm, the nano-composite particles of the antitumour agent TAS-103 are expected to be effective for treatment of lung cancer, when these particles are delivered directly into the lungs [78]. However, there would be several problems in this treatment strategy; namely, lung tissue has a low water content, and the viscosity of the aqueous phase becomes high by dissolving the sugars derived from the composite particles. Hence, further studies are necessary for developing the nano-composite particles for inhalation treatment.

Surface modification of nanoparticles contributes to efficient delivery to cancer cells. Transferrin interacts with transferrin receptors, which are overexpressed in various types of cancer cells owing to their high metabolism [79, 80]. Coupling of transferrin to nanoparticles potentiates their antitumour activity by increasing their uptake by human gastric cancer cells [81]. In addition, transferrin-dependent uptake of the particles by cancer cells results in sustained intracellular retention of drugs [82].

5.6.3 INHALATION THERAPY FOR COPD

Current treatment of COPD for prevention of its progression is performed with a bronchodilator, which is commonly used for asthma. COPD shows emphysema due to chronic inflammation initiated from the responses by neutrophils and macrophage cells towards tobacco smoke, leading to decreased numbers of alveoli due to destruction of the lung tissue beyond the terminal bronchiole [83, 84]. Hence, inhibition of the inflammatory responses and induction of regeneration of the lung tissue would contribute to the treatment of COPD.

As vitamin A is likely to be associated with early lung development and alveolar function, supplementation with it could be an efficient therapy for COPD [85]. In addition, all-*trans*-retinoic acid (ATRA), a derivative of vitamin A, is expected to be a candidate for treatment of COPD, because ATRA increases the population of bone marrow-derived cells in the lung alveoli, leading to lung regeneration based on the differentiation of the recruited cells [86, 87]. As a massive intake of vitamin A induces significant toxicity, the limit on intake has been set at around 3000 μg per day [88, 89]. Hence, local administration of vitamin A or its derivatives to the lungs is expected to prevent their significant side effects and to be beneficial for the treatment of COPD.

ATRA is reported to be well enclosed into various types of nanoparticles consisting of PLGA, deoxycholic acid-conjugated dextran and lipids [90–92]. Pulmonary administration of liposomal ATRA results in down-regulation of the tissue-matrix-destroying mediator metalloproteinase-9 and up-regulation of the tissue-protecting factor called tissue inhibitor of metalloproteinase-1 [93]. However, the effectiveness of ATRA itself towards COPD is controversial, because no clear improvement of lung function following treatment has been reported [94].

5.7 SUMMARY

As lung tissue is an essential one for gas-exchange, pulmonary diseases may result in death. Both structure and function of the lungs are well suited to avoid invasion by pathogens and toxic particles. Given that particles containing therapeutic agents are also regarded as toxic materials by the bio-defence system of the lungs, smart strategies and highly advanced technologies are required to deliver the particles for medical use to the distal lung alveoli for the treatment of intractable pulmonary diseases, such as TB, lung cancer and COPD. Current research employing various technologies has shown some success in the efficient delivery of inhalable particles to the distal lung tissue. Although inhalation therapy is still in its development stage, the use of inhalable particles is promising for treatment of pulmonary diseases.

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