Chapter 17
Targeted Delivery of Surface-Modified Nanoparticles: Modulation of Inflammation for Acute Lung Injury

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Abstract Nanocarriers have been widely employed in the diagnosis and treatment of various diseases. The drug release kinetics and pharmacodynamics could be adjusted by changing the materials, designs, and physicochemical properties of the carriers. Furthermore, the carrier surface could be modified to minimize the particle clearance, increase the circulation duration, escape the biological protective mechanisms, penetrate through physical barriers, and prolong the residence of the drug at the target site. Among lung diseases, acute lung injury has been considered life-threatening with approximately 190,000 cases and 74,500 deaths per year in the USA. Numerous researches have reported the efficacy of drug-encapsulated nanoparticles in the treatment of acute lung injury. The use of nanoparticles could help minimize the effect of airway defenses in the lung, thus provides a prolonged retention, sustained drug release, and targeted delivery to the lung tissues. Meanwhile, the toxicity of nanoparticles in the lungs needs to be investigated thoroughly to alleviate the safety concerns. In this chapter, we discuss the targeted pulmonary delivery of surface-modified nanocarriers to efficiently treat acute lung injury.

Keywords Nanocarriers · Acute lung injury · Surface-modified nanoparticles · Pulmonary delivery · Toxicity

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Y. V Pathak (ed.), Surface Modification of Nanoparticles for Targeted Drug Delivery, https://doi.org/10.1007/978-3-030-06115-9_17
1 Nanoparticles

1.1 Introduction of Nanoparticles

Targeted nanoparticles especially nano-sized drug delivery systems were first introduced into the field of medicine in the nineteenth century. In the 1960s, nanoparticles were developed for vaccination delivery [1]. From then on, nanotechnology has been furthered in numerous clinical trials and several products available on the market, particularly in the diagnosis and treatment of cancer [2, 3]. Also, a wide range of nanocarrier types has been fabricated and optimized as advanced drug delivery systems.

Nanoparticles have been fabricated from various macromolecular materials with the size ranging from 1 to 200 nm to drive therapeutic agents into the body tissue [4]. A wide range of diseases has been targeted with nanoparticles such as cancer [5] or tuberculosis [6]. Despite a long history of research and development, the number of marketed products with nanoparticles remains limited. The first commercial product was Abraxane® (available in 2005), which was formulated as an injectable albumin nanoparticle suspension with paclitaxel to treat cancer [7] (Table 17.1).

1.2 Properties of Nanoparticles

Nanoparticles have been commonly used as drug carriers where the active therapeutical ingredients could be dissolved, entrapped, encapsulated, adsorbed, or attached to the particles using various fabrication methods including solvent evaporation, nanoprecipitation, or multiple emulsions [7–9]. The drugs can be retained in the particles with covalent, electrostatic interactions or the like [10]. These solid colloidal nano-sized particles are constructed with biocompatible and biodegradable materials that decompose at a certain rate in the body. The degradation process of these materials could be adjusted to alter the drug release and the physicochemical properties of the nanoparticles [11].

The circulation, absorption, and elimination of nanoparticles in the human body vary depending on the properties of the particles and the targeted tissues. Blood–brain barrier allows nanoparticles with size less than 1 nm to efficiently pass through while nanoparticle of 6 nm dimension could penetrate the continuous capillaries in muscles, lungs, and skin tissue. With the size range from 40 to 60 nm, nanoparticles could escape the fenestrated capillaries in kidney, intestine, and endocrine or exocrine glands [12]. There has been found agglomeration of large nanoparticles (size of more than 600 nm) in liver, spleen, and bone marrow [13]. The electrostatic properties of nanoparticles could be employed to facilitate or inhibit the particle endocytosis. Positively charged nanoparticles could be attached rapidly to cells with the negatively charged surface [12]. Nanoparticles have long been used as imaging agents and drug carriers due to their numerous advantages such as (1) large
Table 17.1 List of approved nanopharmaceuticals

| Brand name           | Active ingredient               | Properties                                                                 | Indication                                                                 | Provider                                      | Approval               |
|----------------------|--------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------------------------------------------|------------------------|
| Liposomes            | Amphotericin B                 | Amphotericin B encapsulated in liposomes for injection                     | Systemic fungal infections (IV)                                            | Sigma-Tau Pharmaceuticals, Inc.               | FDA 1997               |
|                      | DaunoXome®                     | Daunorubicin citrate-encapsulated liposome for injection                   | HIV-related Kaposi’s sarcoma (IV)                                          | Galen US Inc.                                 | FDA 2007               |
|                      | DepoCyt®                       | Cytarabine-encapsulated in multivesicular liposomes for injection          | Lymphomatous malignant meningitis (IV)                                     | Sigma-Tau Pharmaceuticals, Inc.               | FDA 1999/2007          |
|                      | AmBisome®                      | Amphotericin B encapsulated in liposomes for injection                    | For the treatment of pain following major surgery                          | Endo Pharmaceuticals Inc.                     | FDA 2004               |
|                      | DaunoXome®                     | Daunorubicin citrate-encapsulated liposome for injection                   | AIDS-related Kaposi’s sarcoma, multiple myeloma, ovarian cancer            | ALZA Corporation                              | FDA 1995               |
|                      | DepoDur®                       | Morphine sulfate-encapsulated in multivesicular extended-release liposomes for injection | For the treatment of pain following major surgery                          | Crucell (former Bena Biotech Ltd.)           | FDA 2004               |
|                      | Marqibo®                       | Vincristine sulfate encapsulated in liposomes                             | Nonmetastasizing resectable osteosarcoma (IV)                              | Talon Therapeutics, Inc.                      | FDA 2007               |
|                      | Mepact™                        | Mifamurtide incorporated into large multilamellar liposomes               | The first line treatment of metastatic breast cancer in adult women (IV)   | Takeda France SAS                              | FDA 2009               |
|                      | Visudyne®                      | Verteporfin in liposomes for injection                                     | Photodynamic therapy of wet age-related macular degeneration, ocular histoplasmosis syndrome (IV) | Novartis AG                                  | FDA 2000               |

(continued)
| Brand name | Active ingredient | Properties | Indication | Provider | Approval |
|------------|------------------|------------|------------|----------|----------|
| **Nonliposomal lipid-based formulations** | | | | | |
| Abelcet® | Amphotericin B | Amphotericin B complexed with two phospholipids (l-α-dimyristoyl phosphatidyl choline and l-α-dimyristoyl phosphatidyl glycerol) | The treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy | Exelead, Inc. | FDA 1995 and 1996 |
| Amphotec® | Amphotericin B | Complex of amphotericin B and cholesteryl sulfate | The treatment of invasive aspergillosis | InterMune, Inc. | FDA 1996 |
| **PEGylated proteins, polypeptides, aptamers** | | | | | |
| Adagen® | Pegademase bovine | PEGylated adenosine deaminase | Adenosine deaminase deficiency—severe combined immunodeficiency disease | Leadiant Biosciences, Inc. | FDA 1990 |
| Cimzia® | Certolizumab pegol | PEGylated antibody | Crohn’s disease, rheumatoid arthritis | UCB, Inc. | FDA 2008 |
| Neulasta® | Pegfilgrastim | PEGylated filgrastim | Febrile neutropenia, In patients with nonmyeloid malignancies; prophylaxis (SC) | Amgen Inc | FDA 2002 |
| Oncaspar® | Pegasparagase | PEGylated L-asparaginase | Acute lymphoblastic leukemia | Sigma-Tau Pharmaceuticals, Inc | FDA 1994 |
| Pegasys® | Peginterferon Alfa-2a | PEGylated interferon alfa-2b | Hepatitis B and C | F. Hoffmann-La Roche AG | FDA 2002 |
| PegIntron® | Peginterferon alfa-2b | PEGylated interferon alfa-2b | Hepatitis C | Schering-Plough Corporation | FDA 2001 |
| Somavert® | Pegvisomant | PEGylated human growth hormone receptor antagonist | Acromegaly, second-line therapy | Pharmacia and Upjohn Company, LLC | FDA 2003 |
| Macugen® | Pegaptanib Sodium | PEGylated anti-VEGF aptamer | Intravitreal Neovascular age-related macular degeneration | Valeant Pharmaceuticals International, Inc. | FDA 2004 |
| Mircera® | Methoxy polyethylene glycol-epoetin beta | PEGylated epoetin beta | Anemia associated with chronic renal failure in adults | F. Hoffmann-La Roche AG | FDA 2007 |
| Brand name       | Active ingredient        | Properties                                      | Indication                                      | Provider                        | Approval  |
|------------------|--------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------|-----------|
| **Nanocrystals** |                          |                                                 |                                                 |                                 |           |
| Emend®           | Aprepitant                | Aprepitant as nanocrystal                       | Emesis, antiemetic                              | Merck                           | FDA 2003  |
| Megace ES®       | Megestrol acetate         | Megestrol acetate as nanocrystal                | Anorexia, cachexia                              | Endo Pharmaceuticals            | FDA 2005  |
| Rapamune®        | Sirolimus                 | Rapamycin (sirolimus) as nanocrystals formulated in tablets | Immunosuppressant                              | PF Prism C.V.                   | FDA 2002  |
| Tricor®          | Fenofibrate               | Fenofibrate as nanocrystals                     | Hypercholesterolemia, hypertriglyceridemia      | AbbVie Inc.                     | FDA 2004  |
| Triglide®        | Fenofibrate               | Fenofibrate as insoluble drug-delivery microparticles | Hypercholesterolemia, hypertriglyceridemia      | Skye Pharma AG                  | FDA 2005  |
| **Polymer-based nanoformulations** |                          |                                                 |                                                 |                                 |           |
| Copaxone®        | Glatiramer acetate        | Polypeptide consist of four amino acids          | Multiple sclerosis (SC)                         | Teva Pharmaceuticals USA        | FDA 1996/2014 |
| Eligard®         | Leuprolin acetate         | Leuprolide acetate incorporated in nanoparticles | Advanced prostate cancer (SC)                   | Tolmar Therapeutics            | FDA 2002  |
| Genexol®         | Paclitaxel                | Paclitaxel incorporated in micelles             | Metastatic breast cancer, pancreatic cancer (IV) | Samyang Biopharma              | South Korea 2001 |
| Opaxio®          | Paclitaxel poliglumex     | Paclitaxel covalently linked to solid nanoparticles | Glioblastoma                                   | Cell Therapeutics, Inc.         | FDA 2012  |
| Renagel®         | Sevelamer hydrochloride   | Cross-linked poly allylamine hydrochloride       | Hyperphosphatemia                               | Sanofi Genzyme                  | FDA 2000  |
| **Protein–drug conjugates** |                          |                                                 |                                                 |                                 |           |
| Abraxane®        | Paclitaxel                | Paclitaxel-encapsulated nanoparticles           | Metastatic breast cancer, non-small-cell lung cancer (IV) | Abraxis BioScience              | FDA 2005  |
| Kadcyla®         | Ado-Trastuzumab Emtansine | Immunoconjugate                                 | Metastatic breast cancer                        | Genentech                       | FDA 2013  |

(continued)
| Brand name   | Active ingredient | Properties                                                                 | Indication                                                                                           | Provider                      | Approval       |
|-------------|-------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------|----------------|
| Ontak®      | Denileukin diftitox | Recombinant fusion protein of fragment A of diphtheria toxin and subunit binding to interleukin-2 receptor | Primary cutaneous T-cell lymphoma, CD25-positive, persistent or recurrent disease                     | Eisai Inc.                   | FDA 1994/2006 |
| Surfactant-based nanoformulations | | | | | |
| Fungizone®  | Amphotericin B     | Lyophilized powder of amphotericin B with added sodium deoxycholate         | Systemic fungal infections (IV)                                                                     | Bristol-Myers Squibb         | FDA 1966      |
| Diprivan®   | Propofol           | Oil-in-water emulsion of propofol                                           | Sedative–hypnotic agent for induction and maintenance of anesthesia (IV)                             | Fresenius Kabi USA           | FDA 1989      |
| Estrasorb™  | Estradiol hemihydrate | Emulsion of estradiol                                                      | Hormone replacement therapy during menopause                                                         | Exeltis USA, Inc.            | FDA 2003      |
| Metal-based nanoformulations | | | | | |
| Feridex®    | Ferumoxides        | Dextran-coated superparamagnetic iron oxide nanoparticles                   | Liver/spleen lesion magnetic resonance imaging (IV)                                                 | AMAG Pharmaceuticals, Inc.   | FDA 1996      |
| Feraheme™ (Ferumoxytol) | | | | | |
| NanoTherm®  | Iron oxide         | Aminosilane-coated superparamagnetic iron oxide nanoparticles              | Local ablation in glioblastoma, prostate, and pancreatic cancer                                      | MagForce AG                  | Europe 2013   |
| Virosomes   |                   | | | | |
| Gendicine®  | Gene therapy       | A recombinant adenovirus engineered to express wild-type p53               | Treat patients with tumors which have mutated p53 genes. Head and neck squamous cell carcinoma       | Shenzhen SiBiono GeneTech    | People’s Republic of China 2003 |
| Rexin-G®    | Gene therapy       | Gene inserted into the retroviral core of viral genes                     | For all solid tumors                                                                                | Epeius Biotechnologies       | Philippines 2007 |

*FDA US Food and Drug Administration, IV intravenous, SC subcutaneous*
surface-volume ratio, (2) biological mobility, (3) enhanced tissue penetration, (4) drug protection against degradation or loss, (5) sustained and controlled drug release, (6) reduction of dose frequency, (7) improved patient compliance, and (8) increased drug level at the target site [7, 14, 15].

1.3 Surface-Modified Nanoparticles

These days, nanoparticle surface and dimensions have been modified to minimize the particle clearance, increase the circulation time, escape the biological protective mechanisms, penetrate through physical barriers, and prolong the residence of the drug at the target site [7]. Thus, various moieties have been utilized for modification and functionalization of the nanoparticle surface in accord with different stimuli [12].

Nanoparticles could be stimulated by endogenous or exogenous factors. The endogenous stimulus includes redox, enzyme, and pH while light, ultrasound, and magnetic fields have been employed as exogenous factors to manipulate the behavior of nanoparticles [16]. Surface modification and polymeric coating of nanocarriers could allow altering the half-life, biocompatibility, biodistribution, circulation duration, stimuli reactivity, and therapeutic application [10, 17]. Furthermore, the hydrophilicity of nanoparticles was found to primarily determine the rate of particle binding on blood components. Hydrophobic nanoparticles without surface functionalization have been indicated to be eliminated rapidly whereas the circulation was significantly enhanced as these particles were coated with hydrophilic polymers or surfactant to increase the hydrophilicity [18] (Fig. 17.1).

Controlled and sustained drug release from nanoparticles is critical to the therapeutic efficacy. The drug release can be triggered by stimuli or occur in sustained mode over a certain period of time [10]. The drugs could diffuse out of the particles or the particles might slowly and gradually degrade to release the drug load. The

![Fig. 17.1 Types of nanocarriers. Source: Author’s representation](image)
stimuli-responsive release of drug from nanoparticles may facilitate the drug accumulation in the targeted tissues. These stimuli could be generated by a modification in the biological environment including cell environment, pH alteration, and disease-related enzymes or external physical forces such as light, ultrasound, heat, electrical, and magnetic fields. Ultrasound-sensitive microbubbles have been employed to release therapeutic agent to the local targets [19]. Microbubbles fabricated from lung surfactants caused a significant enhancement in drug targeted deposition as compared to lipid-only microbubbles [20]. Interestingly, the application and control of magnetic fields could drive aerosol droplets encompassing super-paramagnetic iron oxide to the targeted locations in the mice’s lungs in vivo [21].

1.4 Potential Toxicity of Nanoparticles

A comprehensive understanding of biocompatibility, biodistribution, and degradation of nanoparticles is expected to properly utilize the particles [10]. The physical properties including geometry, dimensions, surface charge, and morphology have been found to alter the therapeutic effects of nanoparticles [22]. In particular, rod-shaped particles were more toxic than spherical particles [23]. Long fibers could less likely be captured by macrophages, thus minimize their elimination from the system and cause inflammation [24]. Surface functionalization of nanoparticles could change their biodistribution, effectiveness, and toxicity. Specifically, biopersistent carbon nanotubes could be modified and functionalized to enhance the hydrophilicity and rapid clearance via renal excretion [25]. A small change in the physicochemical properties of nanoparticles could be exaggerated into significant alteration in the biological response. Thus, the biological safety of nanoparticles needs to be evaluated and monitored with care [10].

1.5 Conclusion

Nano-sized carriers are a promising platform for controlled drug delivery due to their dimensions, permeability, and drug loading. Furthermore, surface functionalization could be used to enhance the targetability as well as to reduce the toxicity [12]. The nanomaterials could be coated or conjugated with various segments to prepare multifunctional and stimuli-responsive drug delivery system [12] which allows to modify drug release profile, specific targeting, compatibility, and several other advantages. More and more clinically effective nanocarriers are expected in the market in the future.
2 Acute Lung Injury

2.1 Pulmonary Drug Delivery

The lung offers several beneficial properties for rapid and efficient drug delivery due to the large alveolar surface area, a thin layer of the epithelial barrier, extensive blood circulation, avoidance of the first-pass hepatic metabolism, and low proteolytic activity in the alveolar space [26–29]. The metabolic activities in the lung are significantly lower than that in the gastrointestinal tract and the liver [10]. These properties not only enhance the systemic drug delivery but also improve the efficacy of treatment of lung diseases. Furthermore, drug administration via the lung has been preferred due to its noninvasiveness and the possibility for self-administration.

Despite the aforementioned advantages, there are only limited products on the market for lung delivery. The only inhalable product of therapeutic protein on the market is Pulmozyme® (dornase alfa, Genentech Inc., San Francisco, CA, USA). Exubera (Inhalable insulin, Pfizer, New York, NY, USA) was approved by US Food and Drug Administration in 2006, but later withdrawn from the US market in 2007 due to the deficiency of consumer demand.

The lung has an effective mechanism of clearing external agent, thus making it challenging to deposit drugs in a region in the lung. Inhalable particles could be eliminated from the lung by two mechanisms. Firstly, particles can be cleared by the moving patches of mucus layer in the conducting zone of the lung. The clearance would be more efficient in lung diseases with an increase in mucus production and thickness [10]. Secondly, in the deep lung, macrophages (on the air side of the alveolar cells) could engulf and digest to remove insoluble particles rapidly.

2.2 Introduction of Acute Lung Inflammation

An acute lung injury (ALI) is a disease in which the lungs could not sufficiently provide oxygen to the body, causing low levels of oxygen in the blood (hypoxemia). The leading causes of ALI have been found to be pneumonia, sepsis, lung trauma, burns, near drowning, and other condition related to inflammation or damage to the lungs. As first described in 1967, Acute lung injury (ALI) was diagnosed with acute respiratory distress, cyanosis refractory to oxygen therapy, decrease lung compliance, and diffuse infiltrates on chest radiography [30]. In 1988, this definition was expanded to encompass the level of positive end-expiratory pressure, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, the static lung compliance, and the degree of infiltration evident on chest radiography [31]. Later, the lung injury score was included to evaluate the severity level of the disease in clinical trials [32]. American-European Consensus Conference Committee proposed a new definition that classifies the severity of lung injury and segregates the patients into two groups: acute lung injury (less severe hypoxemia) and acute respiratory distress syndrome (more severe hypoxemia) [33].
Recent surveys reveal that approximately 190,000 cases of ALI with 74,500 deaths per year in the US [34]. This life-threatening disease has been influencing millions of people every year over the world [35]. The in-hospital mortality rate of ALI was estimated to be 38.5% [34], which could be reduced to 31% using low-tidal volume ventilation [36, 37]. The primary cause of death was attributed to sepsis or multiple organ dysfunction syndromes.

### 2.3 Mechanism and Properties of Acute Lung Injury

ALI could occur due to either direct or indirect mechanical, toxic, infectious, or inflammatory challenges to the lung [38]. The most common cause of ALI was severe pulmonary sepsis, following by trauma, aspiration, multiple blood transfusion, acute pancreatitis, inhalation injury, and drug toxicity [39].

The interaction and communication between different cell types have been investigated to discover the pathology of ALI. Mechanism of ALI most likely relates to cell death in necrosis and apoptosis [35]. In lung injury, cell death could occur based on oncosis [40], cathepsin-dependent cell death, or autophagy. A wide range of cell types is associated with ALI such as alveolar epithelial and vascular endothelial cells (change in permeability to cause edema formation and alveolocapillary injury) and platelets and immune cells (inflammatory response) [41–44]. ALI is involved in a prothrombotic and antifibrinolytic shift that facilitate fibrin deposition, thus, advance the inflammation [45].

ALI and ARDS are represented by bilateral exudative chest infiltrate which could be diagnosed by roentgenograms [44, 46]. ALI can progress rapidly from an initial stage of a leaky edematous lung to a proliferative phase with deposition of fibrin and a reduction in respiratory compliance, and to a fibrotic phase with scarring lung. The hallmarks of ALI—protein extravasation and formation of lung edema—were caused by excessive inflammation, alteration in coagulation and fibrin deposition, and increase in permeability of the alveolocapillary barrier [38].

### 3 Nanoparticles to Treat Acute Lung Injury

#### 3.1 Advantages of Nanoparticles for Lung Delivery

The large surface area of alveolar, a thin layer of epithelial barrier, and a dense network of blood vessels facilitate the delivery of various therapeutic agents [47]. The use of nanoparticles could help to minimize the effect of airway defenses in the lung. Once delivered to the lungs, nanoparticles could have a prolonged retention, sustained drug release, and targeted delivery to the lung tissues [10, 48]. Extensive studies have been conducted for the pulmonary delivery of polymeric nanoparticles for various compounds including asthmatic drugs [49, 50], antituberculosis drugs [51],
and anticancer drugs [52, 53]. Also, liposomal nanoformulations have been investigated and evaluated to be a promising platform for drug delivery. Currently, multiple liposomal formulations are FDA-approval products available on the market while several others are studied in clinical trials [54]. Liposome has a major advantage of being fabricated from compounds compatible and endogenous to the lung (such as lung surfactants), thus becoming a preferred pulmonary drug delivery system. Some marketed liposomal products for the treatment of acute respiratory distress syndrome are Exosurf® (Colfosceril Palmitate, GlaxoSmithKline, Brentford, UK) and Alveofact® (Bovactant, Lyomark Pharma, Oberhaching, Germany) [55]. Budesonide-encapsulated liposomes have been developed to deliver the drug at a controlled release rate to maintain the therapeutic concentrations in rat lungs in vivo. This liposomal formulation also helped to reduce the systemic exposure and toxicity [56]. Interestingly, multiple drugs could be combined and delivered to the lung simultaneously using nanocarrier systems. Nanoparticles offer several benefits as they could penetrate the lung more deeply and enter the alveolar areas [10]. Furthermore, nanoparticle-based systems evade macrophage clearance effectively and permeate the lung epithelium. Also, the surface of nanoparticles could be modified and functionalized to enhance the drug bioavailability, to improve the penetration into the mucus layer, and aid targeted delivery [10]. The deposition of nanocarriers could be prolonged by using mucoadhesive materials, for instance, biodegradable polysaccharide chitosan [7]. Yamamoto and colleagues fabricated peptide elcatonin-encapsulated PLGA nanoparticles whose surface was modified with chitosan. Once delivered to the lungs of guinea pigs, the particles caused a significant decrease in blood calcium levels as compared to the initial concentrations. Furthermore, this effect was prolonged and sustained up to 24 h (due to the slow elimination of chitosan-modified particles), which was markedly longer than unmodified particles [57].

3.2 Surface-Modified Nanoparticles for Lung Delivery

The use of surface-modified nanoparticles is beneficial for lung delivery. Brush-shaped nanoparticles have been formed with low molecular weight poly(ethylene glycol) chains (PEG) for a reduction of phagocytosis [58]. Furthermore, PEGylated nanocarriers were found to easily and readily penetrate the mucus layer in chronic obstructive lung diseases [59]. In contrary, chitosan could be used to modify the particle surface to enhance the mucoadhesion and circulation. Thus, chitosan-modified nanoparticles could reside for a longer period at the targeted site to improve the drug uptake, bioavailability, and therapeutic efficacy. This property is particularly desirable for the treatment of nonobstructive lung diseases including allergy and lung cancer [10]. Interestingly, biological fluids could modify the surface of particles to form protein corona whose properties are enhanced as compared to the original particles [60]. Lung surfactant phospholipids have been used to coat nanoparticles to alleviate toxicity as well as to improve cellular uptake [61]. Furthermore, the agglomeration of the particles helps create large agglomerates to be digested by macrophages [62] (Table 17.2).
Table 17.2  Surface-modified nanoparticles for acute lung injury

| Nanoparticles                                                                 | Effect                                                                 | Mechanism                                                                 | Study model         | References |
|--------------------------------------------------------------------------------|**************************************************************************|**************************************************************************|*********************|***********|
| Polydopamine nanoparticles (similar to melanin)                                | Anti-inflammation therapeutic effect on acute inflammation-induced injury | Polydopamine with enriched phenol groups functioned as a radical scavenger to eliminate reactive oxygen species | Murine models       | [63]       |
| Lung-targeting functionalized nano-sterically stabilized unilamellar liposomes loaded with glucocorticoids methylprednisolone | Good particle size distribution, morphology, encapsulation efficiency, and high specificity to the lung. | Reduce the levels of TNF-α, IL-8, and TGF-β1 in rat bronchoalveolar lavage fluid and the expression of NK-κB in the lung tissues, thus alleviate lung injuries and enhance rat survival | Rat               | [64]       |
| Generation IV polyamidoamine dendrimers                                       | The treatment of ischemia-reperfusion-induced acute lung injury          | Dendrimers were taken up in epithelial cells and macrophages.             | Ex vivo rabbit model| [65]       |
| Dry powder formulations of inhalable apigenin-loaded bovine serum albumin nanoparticles | Good aerodynamic properties of the particles and antioxidant activity of encapsulated apigenin | Novel delivery system against lung injury with potential antioxidant activity |                   | [66]       |
| Two-component co-spray dried DMF:D-Man DPIs with high load of dimethyl fumarate | Capability to reach lower airways to treat inflammation in pulmonary diseases | Exhibit excellent aerosol dispersion performance with a human DPI device | In vitro predictive lung deposition modeling | [67]       |
| Human amniotic fluid stem cells labeled with dual-polymer-coated UCNP-PEG-PEI nanoparticles | Display remarkable positive effects on ALI-damaged lung tissue repair. | Recover the integrity of the alveolar-capillary membrane, attenuate transepithelial leukocyte and neutrophil migration, and down-regulate proinflammatory cytokine and chemokine expression | A murine model of acute lung injury | [68]       |

(continued)
Table 17.2 (continued)

| Nanoparticles | Effect | Mechanism | Study model | References |
|---------------|--------|-----------|-------------|------------|
| Poly-lactic-co-glycolic acid nanoparticles-facilitated cDNA delivery | Upregulate pulmonary EpoR expression and downstream signal transduction in rats for 21 days, Attenuate hyperoxia-induced damage in lung tissue based on apoptosis, oxidative damage of DNA, protein and lipid, tissue edema, and alveolar morphology | Targeted pulmonary EpoR upregulation mitigates acute oxidative lung damage | Rat lungs | [69] |
| Nanoparticles based on polyethyleneimine and DNA | When β2-Adrenergic Receptor (β2AR) was applied as the therapeutic gene, PEI/β2AR treatment significantly attenuated the severity of ALI. PEI/DNA nanoparticles could be an efficient agent in ALI treatment. | Attenuate alveolar fluid clearance, lung water content, histopathology, bronchioalveolar lavage cellularity, protein concentration, and inflammatory cytokines in mice with preexisting ALI | Mouse model of ALI induced by lipopolysaccharide | [70] |
| Shell cross-linked knedel-like polymer nanoparticles | The $K_d$ values of the nanoparticle-attached PNAs were about an order of magnitude greater than the free PNAs | Recognize and selectively inhibit of mRNA sequences for inducible nitric oxide synthase (iNOS), which are overexpressed at sites of inflammation | | [71] |
3.3 Factors Affecting Nanoparticles Delivery to the Lung

The deposition and distribution of nanoparticles in the lungs vary depending on several factors such as breathing rate, lung volume, air flow, and particle size [10]. Multiple studies have suggested that particle size plays the most important role in manipulating the distribution and deposition of the particles in the lung. Small particles (size range from 1 to 5 μm) are deposited in the deep regions while inhaled particles (whose size is larger than 10 μm) are found primarily in the oropharyngeal region [72, 73]. A requirement for lung delivery is the proper design of the carrier systems [74]. Pulmonary delivery of inhaled particles is dominated by various factors such as particle size, particle density, and the mass median aerodynamic diameter in which the particle size could guarantee a maximum distribution and deposition of the particle in the deep lung [75]. The rate of clearance is primarily affected by the particle size in the alveolar region. Several studies have been performed to investigate the interaction between nanoparticles and macrophages. Large particle (aerodynamic diameter more than 6 μm) are exhaled without being phagocytosed [76], microparticles (aerodynamic diameter 1–5 μm) are effectively taken up by macrophages, while nanoparticles (aerodynamic diameter less than 200 nm) could penetrate the cellular barrier and the particle phagocytosis by alveolar macrophages can be reduced [48, 77, 78]. These indicate that nanoscale particles could avoid macrophage clearance while being deposited in the deep lung, especially the alveolar regions [10]. However, small particles require a high level of energy for fabrication and disaggregation. Inhaled particles could be deposited in the lung by inertial impaction, sedimentation, and diffusion. The particle deposition is analogous to the settling of spherical particles under gravity force through the air. Nanoparticles, which is not deposited in the lungs, is exhaled to result in a major loss of the delivered dose [79].

3.4 Pulmonary Delivery of Nanoparticles Using Dry Powder Carriers

Proper dry powder formulations and carrier systems have been developed and optimized to deposit nanoparticles to the alveolar regions to enhance the efficacy of their pulmonary delivery [80]. Kawashima and coworkers employed hydroxypropylmethyl cellulose phthalate (HPMCP) nanospheres (hydrophilic nanoparticles) to facilitate the inhalation properties of dry powder pranlukast hydrate [81]. The authors mixed the surface nanospheres and drug powder with lactose. Thus, in the in vitro inhalation test, the emission and dispersibility of surface-modified drug powder increased significantly and the powder was effectively delivered to the deep lung. Kawashima et al. fabricated insulin-loaded PLGA nanospheres. Then, an
ultrasonically assisted nebulizer was utilized to deliver the nanospheres to the trachea of guinea pigs. The authors reported a significant decrease in the blood glucose and a sustained hypoglycemic effect for 48 h. The results were attributed to the controlled release of insulin from the nanospheres and their deposition in multiple regions of the lung [82]. Tsapis and coworkers employed a spray drying method to manufacture large porous particles. Using 1,2-dipalmitoyl-sn-glycero-3-phosphocholine and 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine (surfactants), and lactose, the authors could tailor the physicochemical properties of the spray-dried powder for pulmonary delivery [78]. Interestingly, nanoparticles could be loaded in a carrier matrix. Sham and colleagues dissolved lactose in nanoparticle suspension before spray drying to obtain nanoparticles-incorporated carrier powder. The authors observed a marked change in the particle size and reported the possibility of manipulating the delivery and release of nanoparticles [80]. In another study, Grenha et al. used lactose and mannitol together with a spray drying method to prepare microspheres, which contain insulin-incorporated nanoparticles for pulmonary drug delivery. The drug release from nanoparticles was found to be unaffected by the microencapsulation. Furthermore, this system allows to effectively deliver macromolecules via pulmonary administration [47]. The spray drying technique was also employed by Ely and colleagues to prepare effervescent carrier particles which incorporate ciprofloxacin-loaded nanoparticles. The authors could manage to alter the particle size to maximize the particle deposition in the deep lung. The use of effervescent carrier particles resulted in a marked enhancement in the drug release. Also, they observed an insignificant change in the nanoparticles dimension upon being released from the effervescent carrier particles [74]. Pulmonary administration is a promising platform to deliver nanoparticles carried in dry powders. The nebulization parameters of the matrix should be optimized to minimize particle aggregation and to facilitate the drug delivery into the deep lungs [83].

### 3.5 Pulmonary Delivery of Nanoparticle Suspensions Using Nebulization

Nanoparticles could be delivered by spraying or nebulizing the nanoparticle suspension. Dailey and coworkers formulated a surfactant-free nanoparticle suspension for pulmonary drug delivery. This system could provide a high encapsulation efficiency due to the electrostatic interactions between the drug molecules and the particles. The authors reported that the use of anionic diethylaminopropyl amine-poly(vinyl alcohol)-grafted-poly(lactide-co-glycolide)-contained formulation and an increase in the amount of carboxy methyl cellulose helped to minimize the particle aggregation [84]. Also, Yamamoto et al. prepared and modified the surface of PLGA nanospheres using chitosan to enhance the delivery efficacy of calcitonin to the lung. After the administration of chitosan-modified PLGA nanoparticles to the trachea of...
guinea pigs, the blood calcium was reported to decrease by 80%. Furthermore, the therapeutic level of the drug was sustained for 24 h, which was markedly longer than the unmodified particles. This result could be explained by the mucoadhesion of the nanoparticles to the bronchial mucous and local tissue in the lung as well as the prolonged drug release from the particles. Moreover, chitosan could enhance the drug permeability by loosening the intercellular tight junctions [57]. In another study, itraconazole-loaded nanoparticles were fabricated, dispersed in aqueous media, and nebulized to the murine lung in vivo. This local delivery system led to a high drug concentration in the lung, and a decreased possibility of adverse effects [85]. Thus, nebulizing nanoparticle suspensions is a promising technique to deliver therapeutical agents to the lung. The physicochemical stability of the suspension needs to be maintained for clinical efficacy.

3.6 Local Delivery of Nanoparticles to the Lung

The local delivery of nanoparticles allows to enhance, sustain, and control the drug level at the target site to treat respiratory diseases [7]. Also, this targeted delivery could reduce the required dose, avoid the drug degradation in the gastrointestinal tract (oral administration), and minimize the systemic toxicity. Vaughn and colleagues delivered itraconazole-loaded nanoparticles to treat fungal infections of *Aspergillus fumigatus*. The pulmonary delivery of itraconazole nanoparticles to mice in vivo showed a significantly high and sustained drug concentration in the lung tissues while the drug level in serum was controlled to maximize the treatment efficacy as well as to reduce the possible systemic toxicity [86]. In addition to sustained drug concentrations in the lung, target delivery to certain cells or tissues has been found beneficial. For example, various therapeutic compounds including rifampicin, isoniazid, and pyrazinamide were formulated to target the drug delivery to alveolar macrophages to optimize the treatment of pulmonary tuberculosis [6]. Several studies fabricated and characterized drug-encapsulated nanoparticles for in vivo tests on guinea pigs. PLGA nanoparticles could be delivered to the lungs to maintain the therapeutic levels of the drugs in the plasma as well as in the lungs for a prolonged period of time [87]. Also, this approach allowed to decrease the overall dose and reduce the systemic exposure. Furthermore, the surface of PLGA nanoparticles has been functionalized and modified with wheat germ agglutinin whose bioadhesive properties facilitate its interaction with lectin receptors embedded in the alveolar epithelium to maintain the drug concentration in the lung tissues [88]. This system could result in a sustained drug level in the plasma for 14 days and in the lung for 15 days. Similarly, PLGA nanoparticles which were formulated with sodium alginate and chitosan provided a sustained drug delivery to the lungs of guinea pigs in vivo to eradicate tubercle bacilli from *M. tuberculosis*-infected guinea pigs [51].
3.7 Technical Issues of Nanoparticles to the Lung

Nanoparticles are usually formulated in colloidal solutions for nebulization [7]. However, the storage in an aqueous medium could induce polymer hydrolysis and degradation of drugs. Furthermore, the small dimensions and interactions between particles result in the agglomeration and settling of nanoparticles, thus, cause a reduced functionality of the nebulizer. To overcome these challenges, lyophilization has been employed to dry nanoparticles to obtain a stable storage form which can be later dispersed in an aqueous solution for administration [89, 90]. Stabilizers such as cryoprotectant sugars and surfactants are used to enhance the stability, maintain the characteristics of nanoparticles during lyophilization, and to facilitate resuspension of the dry particles. These stabilizers dissolve in the resuspended solution and are delivered together with the particles.

3.8 Toxicity of Nanoparticles to the Lung

Despite multiple advantages offered by nanoparticles, they still possess some safety concerns. Li et al. reported that polyamidoamine which is a promising material for nanocarriers could cause autophagic cell death in human lung carcinoma cell line (A549 cells) and acute lung injury in mice in vivo, especially the administration of polyamidoamine might lead to mortality [91]. Card and coworkers reviewed the applications of nanoparticles for imaging, diagnostic, and therapeutic use in the lung [92] and stated that several nanomaterials could cause inflammation and fibrosis in the lung. Toxicity of nanoparticles in the lungs has been evaluated in the environmental health field, especially “ultrafine” particles with the aerodynamic diameter less than 100 nm [7]. The nanoscale dimension of ultrafine particles, on the one hand, provide the therapeutic application, on the other hand, might result in toxicity and undesirable health effects. Ultrafine particles could penetrate epithelial and endothelial cells, be taken up efficiently by cells, and distributed in bone marrow, lymph nodes, spleen, liver, heart, the central nervous system, and ganglia [93–95]. The biological activity of nanoparticles could lead to inflammatory and oxidative stress reactions. Several authors have reviewed the effects of physicochemical properties of nanoparticles such as dimensions, surface charge, geometry, and lipophilicity on their efficacy in vivo [96–99]. The toxicity of nonbiodegradable nanoparticles could be markedly different from those biodegradables. There is an insignificant interaction between biodegradable materials and biological systems. Moreover, the speed of degradation of biodegradable nanoparticles leads to a certain variation in the toxic responses. In particular, biodegradable PLGA nanoparticles resulted in markedly lower inflammatory response than nonbiodegradable polystyrene nanoparticles [100]. Nanoparticles could translocate from the lung to other organs to cause adverse reactions in those organs. The toxicological potential of nanoparticles is negatively correlated with the particle size. Certain levels of
toxicity have been observed with inhalable single-wall carbon nanotubes (SWCNT) [85]. Warheit and colleagues investigated the toxicity of SWCNT on rats in vivo and reported that a high-dose pulmonary exposure led to mortality after 24 h. Pulmonary delivery of SWCNT caused multifocal granulomas, which indicated the nonuniform distribution and translocation of SWCNT-induced toxicity in rats [101]. Similarly, Shvedova et al. reported inflammatory responses in the lungs of mice after exposure to SWCNTs. The toxicity could progress to a reduction of pulmonary function as well as increased vulnerability to infection [102].

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