Novel drug delivery systems and significance in respiratory diseases

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1 Introduction

Chronic respiratory disorders (CRDs) comprise the group of diseases that affect the lungs, airways, and other associated structures. The World Health Organization (WHO) has categorized CRDs among the leading causes of global death and disability burden affecting people of all socioeconomic classes. The five most common diseases responsible for respiratory impairment and illness are asthma, chronic obstructive pulmonary disorder (COPD), tuberculosis (TB), lung cancer, and acute respiratory tract infections [1]. According to the WHO estimate, about 235 million people around the world currently have asthma, and more than 3 million people die every year from COPDs. This global disease burden has given rise to the clinical need for developments of delivery systems and tools aimed at the efficient prevention and treatment of these respiratory diseases.

The most common and ancient method of drug delivery to the lungs and airways has been through inhalation. The drugs delivered by inhalation have either of the three main purposes: prophylaxis, topical or systemic disease treatment, and therapy management. Inhaler devices like nebulizers, metered-dose inhalers, dry powder inhalers, and other aerosol-based device technologies are used for delivering drugs. Delivery to lungs through inhalation provides targeted delivery, which requires low drug doses to be delivered as compared with systemic delivery. The targeted approach reduces the systemic side effects caused due to delivery approaches like oral dosage and injections and enhances the therapeutic index by local delivery to the diseased site. The inhalation delivery method is also used for alveoli-based systemic administration owing to the large surface area of the human lungs. It has been found that drugs are more rapidly absorbed through lungs as compared with other noninvasive delivery methods. But rapid diffusion to blood through epithelia is often accompanied by rapid clearance of small molecule drugs and metabolic degradation of peptide therapeutics, thereby reducing the therapeutic efficiency of the inhaled drugs [2].

Pulmonary drug delivery refers to the systems aimed at targeting the delivery of aerosols directly to epithelial cells and respiratory epithelium by means of inhalation. Based on the desired drug release characteristics, the design of the aerosol formulation is varied to provide prolonged retention or rapid absorption. This pulmonary delivery system can be categorized into immediate-release, controlled-release, and sustained-release systems. These systems vary in their polymeric composition and the excipients. The controlled- and sustained-release pulmonary systems are designed to have advantages like a reduced drug dose, improved therapeutic efficiency, enhanced patient compatibility, quick onset of action, bypassing the hepatic metabolism, localized delivery, reduced systemic side effects, prolonged action, and cost-effective treatment [3]. These delivery systems consist of particle-based technologies like microparticles, nanoparticles, micelles liposomes, and protein nanoparticles, which would be briefly introduced in this chapter.

Despite the discussed advantages of pulmonary delivery systems, the delivery to lungs through these devices pose some serious challenges that need to be addressed by the pharmaceutical industry and research community. Firstly the highly evolved defense mechanism of respiratory passage to fight against foreign particles treats the delivered drug carriers as foreign, thereby trying to prevent their deposition to lungs, remove them, or inactivate them if deposited [4]. Secondly the patients' inability to adhere to the prescribed dosage regimen by making proper use of inhaler devices is another challenge that requires attention [5].

This chapter would focus on the mechanisms of drug disposition and absorption through lungs and ideal characteristics of particle-based pulmonary delivery systems, thereby giving a broad idea about such systems. Later on the novel systems that have been developed for controlled and targeted delivery to respiratory disease sites would be discussed in brief. In the end the currently marketed systems and novel patented systems would be summarized, thereby giving an insight into the required delivery systems and the future research prospects.

2 Novel pulmonary drug delivery systems—An overview
2.1 Mechanisms for pulmonary drug administration

The drugs can be primarily delivered by pulmonary delivery systems using two approaches:

(a) Intranasal delivery
(b) Oral inhalative delivery
  - intratracheal inhalation
  - intratracheal instillation

Intranasal delivery refers to the administration of drugs to lungs through the nasal passage, that is, nose-to-lungs aerosol delivery. The intranasal delivery can prove to be advantageous in cases where frequent dosing is required. The method being non-invasive can be used by the patients without external assistance while not interfering

with the daily routine of the patients. Intranasal delivery has often observed to be employed for gas delivery with techniques like nasal high flow therapy, and low flow therapy [6]. Despite the advantages offered by intranasal delivery, the behavior of the nose as an effective particle filter hampers the efficient delivery of conventional aerosols with size ranging from 3 to 7 µm. The nasal route has been shown to exhibit concentration loss as high as 85% while delivering small particles [7, 8].

Oral inhalative delivery is found to be far more effective when compared with intranasal administration in the delivery of small-sized particles with concentration loss as less as 20% [9]. Intratracheal instillation is the method of pulmonary delivery most commonly employed in laboratories for evaluating the pulmonary and systemic effectiveness of delivery systems in preclinical animal studies. In this method, drug solution or dispersion is delivered by means of a syringe, making the method simple, inexpensive, and fast while delivering quantifiable drug amounts. Despite the advantages, intratracheal instillation cannot be practically used in humans physiologically, hence limiting its application to animal studies only [10]. Contrary to this, intratracheal inhalation uses aerosol technology to deliver drug-carrying particles to the lungs with better penetration and uniform drug distribution. The deposition of the drug into lungs and airways using aerosol inhalation techniques generally occurs by three common mechanisms known as inertial impaction, sedimentation, and Brownian diffusion, as described in Fig. 1. Reference source not found [11]. The deposition of drug particles in different regions of the respiratory tract is a complex phenomenon and depends on factors like particle size, the flow of air, and the respiratory region [12]. The mechanisms are briefly discussed here:

- **Inertial impaction**: As the name suggests, this phenomenon occurs when the inertia of particles prevents them from changing their course of movement when
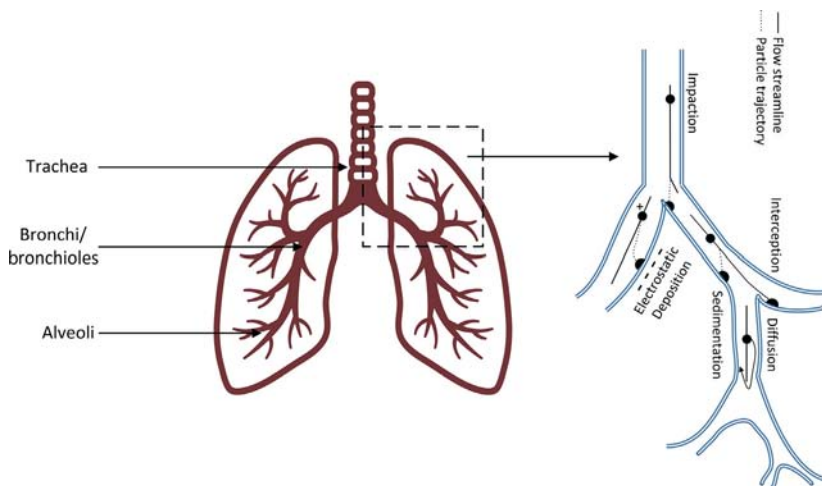
FIG. 1

Schematic representation of the lungs and deposition mechanism of aerosol particles.

the direction of bulk airflow changes. This change in the direction of airflow occurs whenever a bifurcation in the airways is reached. The particles are not able to change their flow direction owing to their momentum and therefore strike against the wall and get deposited. At each bifurcation the particles tend to change their paths from the original air streamline direction, ultimately colliding against the airway walls and getting deposited. Inertial impaction is the major deposition mechanism observed in the upper respiratory tract regions especially near the bronchial area, thus accounting for major deposition in these areas. Impaction-based deposition is generally observed in particles with large aerodynamic diameters. Particles with a diameter larger than 3 μm and traveling near the airway walls are most prone to inertial impaction. The main factors affecting impaction are air velocity, particle mass, particle size, hyperventilation, and frequency of respiration. The chances of impaction increase with the increase in particle momentum, which is basically increase in the particle mass and flow velocity. This mechanism leads to the filtration of particles greater than 5 μm in the upper respiratory tract regions like trachea and bronchi. The particles smaller than 3 μm do not undergo inertial impaction [13].

- **Gravitational sedimentation**: This phenomenon includes settling down of small particles under the influence of gravity on the walls. Particles with aerodynamic diameter ranging from 1 to 8 μm deposit through this mechanism. This type of deposition is observed in small airways and alveolar regions of the lungs wherein the distance between the particles and the walls is very less. Breath-holding plays an important role in this type of deposition mechanism. Breath-holding allows the particles that have penetrated deep into the lungs enough time to settle down due to gravity and thus get deposited. The event of gravitational sedimentation occurs when the gravitational force acting on the particles exceeds the air resistance, thereby causing the particles to sediment. The rate at which sedimentation occurs, therefore, depends on the terminal settling velocity of the particles. Particles with higher aerodynamic diameters are more prone to sedimentation. Hygroscopic materials that tend to absorb moisture on their way tend to increase their aerodynamic diameter size, thereby undergoing sedimentation-based deposition. The probability of sedimentation increases with the increase in the particle diameter and residence time of the particle in the airways, whereas it decreases with the increase in breathing rate [12].

- **Brownian diffusion**: In the case of small particles, deposition occurs through the diffusion mechanism, which is based on the Brownian motion principle. Particles with a diameter less than 0.5 μm undergo this kind of deposition. This phenomenon is controlled by particle geometry rather than the aerodynamic diameter, as in the case of impaction and sedimentation. Diffusion can be defined as the movement of particle from high concentration area to low concentration area by means of Brownian movements. Moreover, the Brownian movement of small particles can be defined as the random motion of particles, which results due to collision with gas molecules applying nonuniform

pressures on the particles' surface. Deposition by diffusion generally occurs in the nasopharynx region and in the small airways of alveolar regions, bronchioles in the lungs where the airflow is less as compared with other regions. The diffusion-based deposition decreases with the increase in the aerodynamic particle diameter in contrary to that of impaction and sedimentation. The diffusion coefficients of the particles also play a major role in deposition through this mechanism [12].

Apart from these major mechanisms, some other phenomena like interception, turbulent mixing, and electrostatic precipitation also control the deposition of inhaled drugs into the lungs. Deposition through interception takes place when the particles come in contact with airways owing to their shape or size and then get deposited. This deposition is not like impaction where particles deviate from the main airstream and strike. This phenomenon occurs mostly for fibers in small airways wherein they easily come in contact with airways due to their shape. Another mechanism that dictates deposition is electrostatic precipitation, which causes deposition based on electrical charges. Charged particles present near the airway surfaces create a charged atmosphere that attracts the oppositely charged particles near the airways and leads to deposition due to electrostatic attraction. Another mechanism known as turbulent mixing dictates the particle deposition in upper respiratory regions with large airways. Turbulent mixing is referred to as the irregular fluctuations experienced by the particles of fluid in turbulent motion [14]. These fluctuations lead to the constant change in the flow velocity and flow direction of the particles, thereby leading them to strike against the airway wall and get deposited.

2.2 Strategic criteria for particle-based pulmonary delivery systems

The discussion about the drug deposition mechanisms in the previous sections imply that the drug delivery systems should follow certain criteria to deliver the drug to the desired location in the respiratory tract while maintaining the therapeutic efficiency and desired release rate. As discussed earlier the inhalation is based on aerosolization techniques wherein aerosols consist of uniform-sized particles, further incorporating drug carriers/vehicles. To begin with the physicochemical properties of the particles play a pivotal role in determining the deposition, flow behavior, absorbance, and clearance rate of the system when administered through inhalation. Moreover, the properties of the aerosol formulation also affect efficient delivery. Some of the most important characteristics that should be taken care of in case of the pulmonary delivery system are discussed as follows:

- **Size of the particles in aerosols**: Attempts have been made by pharmaceutical industries to form homogenous aerosol formulations with monodispersed particles. Despite the efforts the aerosols generally exhibit a wide range of particle size distribution while also affecting the shape of the particles. As mentioned earlier the difference in particle size and shape may lead to

deposition of these particles in several undesired regions of the respiratory tract. Thus it is very important to obtain a monodisperse aerosol. An ideal aerosol system with monodispersed particles is considered to have a geometric standard deviation (GSD) of 1. But due to difficulties in the formulation of ideal aerosols, in practice, aerosols with GSD less than 1.22 are considered to be acceptably monodisperse, and any system with greater GSD is either polydispersed or heterodispersed. Thus the target of the manufacturer and researchers should be to obtain a monodisperse aerosol system with GSD less than 1.22 [15].

- **Physical stability**: One of the vital factors that require attention is the physical stability of aerosol suspensions. The aerosols generally consist of very high concentrations of particles in a small volume, which leads to several interparticle interactions like repulsion and aggregation. These interactions might lead to suspension instability and particle aggregation during different storage conditions, thereby performing the product performance when inhaled [16]. This factor is particularly important for particles generated by systems like dry powder inhalers, wherein spray drying is used as the common method. Many of the compounds that are spray-dried are amorphous in nature, and these, when stored in high humidity conditions, tend to gain moisture and exhibit an increase in aerodynamic diameter [17]. This moisture gain leads to degradation of the aerosolization owing to enhanced capillary forces among the particles. Thus, to avoid this kind of instabilities, excipients such as mannitol, trehalose, and lactose are added to the aerosol formulations to maintain long-term physical stability and improve the aerosolization performance [18].

- **Particle density and shape**: The density and shape of the particle also play an important role in determining the aerosolization and deposition mechanisms. As stated earlier the deposition mechanism followed by the particles depend on the aerodynamic diameter of the particles. The calculation of aerodynamic particles takes into consideration the density and the shape factor of the respective particles, thereby rendering these factors as significant. Particles of different shapes generate different drag forces and terminal settling velocities, thereby affecting the aerodynamic diameter that is again related to deposition mechanism. An increase in the surface roughness on account of shape change of particles has been found to decrease the aerodynamic diameter, which enables the particles to reach in deeper areas of lungs when compared with that of spherical particles [19]. It has also been observed that elongated particles exhibit a tendency to be suspended in the air for a longer period, which therefore can travel to deeper areas. Contrary to this, highly elongated particles also experience interception-based deposition [20]. Another phenomenon affected by particle shape is the interparticulate interactions. These interactions are based on van der Waals force, and thus the particle shape that allows minimum exposure area will lead to minimum interparticle interactions, thereby preventing particle aggregation and improving aerosolization performance [21]. Elongated particles exhibited higher attraction forces thereby not suitable for aerosolization [22].

- **pH and osmolarity**: One of the challenges often faced during the formulation of aerosols is the maintenance of optimum pH and tonicity. Aerosol formulations with acidic pH and nonisotonic nature have been shown to induce bronchoconstriction, which is one of the major concerns while delivering aerosols to asthma patients. Lungs have been observed to exhibit limited buffering capacity, unlike the gastrointestinal tract. Thus one of the considerations while formulating should be pH and osmolarity management. Several salts like sodium chloride can be added to the formulations to maintain the osmolarity of the aerosols to around 300 mosmol/L. In addition, HCl, citric acid, phosphate, and NaOH are used to adjust the pH of the aerosol solutions to neutrality [23].
- **Viscosity**: Another factor that affects the output of aerosol formulations is viscosity. The droplet size is directly affected by the viscosity of the solution. It has been found that the increase in the viscosity of the solution leads to increased droplet size, thereby decreasing the output of the nebulizers. The decrease in temperature leads to an increase in the solution viscosity, which in turn affects the particle size, also modifying the deposition mechanism [24].

2.3 General types of pulmonary drug delivery devices

The delivery device plays a major role in the successful pulmonary administration. There has been remarkable research and development in the field of advanced systems for pulmonary administration. The selection of the delivery device is a very significant parameter in formulation design and is based on the desired site of administration in the respiratory tract. The device selected must have suitable characteristics enabling it to generate particles of appropriate aerodynamic diameter so as to deliver them to the desired locations in the lungs. The three most commonly used delivery devices for pulmonary administration are as follows:

- Pressurized metered-dose inhalers.
- Dry powdered inhalers.
- Nebulizers.

Pressurized metered-dose inhalers (pMDIs) are the most common delivery device employed for the treatment of respiratory tract diseases like chronic obstructive pulmonary disorder and asthma. All the inhalable drug classes are available for administration in the form of pMDIs either as a single formulation or combination of two or more drugs. In spite of the pMDIs being most commonly prescribed for obstructive respiratory diseases, it is not easy for patients to use this device correctly [25]. Conventionally the pMDIs consist of structural components like metal canister, metered valve, actuator, and mouthpiece [26]. The metering valve allows the delivery of precise amounts of aerosol after every actuation. The formulation for the pMDIs consists of either suspension or solution in the combination of suspending agents, surfactants, cosolvents, excipients, and propellants. When the drug particles reach the air, the difference between the boiling temperature of the formulation and the

room temperature leads to the formation of aerosolized droplets due to evaporation. The aerosolized particle size varies from product to product [27].

Dry powdered inhalers (DPIs) are another class of devices used for pulmonary delivery that require minimum coordination between the process of actuation and breathing for delivery of powdered drugs to respiratory tracts [28]. DPIs have greater chemical stability as they consist of a dried form of the medications as compared with that of suspensions or solutions in the case of pMDIs. However, the formulation and manufacturing of dried powder particles with appropriate characteristics to enable aerosolization and pulmonary delivery is complex [29]. Conventionally the dry powder consists of micronized drug particles in association with the large-sized excipients like lactose, sucrose, and glucose. Different varieties of DPIs are available like single-unit dose, multiunit dose, and multiple reservoirs. The energy required by the DPIs for drug delivery is derived from the inspiratory efforts of the patients. The structural components of DPIs include mesh, cyclone, manifold, and a spiral chamber. These components must be able to deaggregate the drug-excipient aggregates by utilizing the inhalation force. The inspiratory force required varies from product to product, but a minimum effort of 30–60 L/min is recommended [30].

Nebulizers are the devices used to generate aerosol droplets ranging from 1 to 5 μm aimed at inhalation-based pulmonary delivery. Two different kinds of nebulizers are generally used: jet and ultrasonic nebulizers. These two types of nebulizers differ in the type of force that they utilize to generate aerosols from liquid suspension/solution. Nebulizers do not require coordination between inspiration and actuation and thus can be used for a variety of patients who are unable to use pMDIs and DPIs. Moreover, nebulizers have the ability to administer large doses [31]. Jet nebulizers use the pressure-based mechanism to generate small aerosol particles, whereas ultrasonic nebulizers use sound waves to break large droplets to small aerosol droplets. Some factors that require to be optimized in the case of nebulizers for optimum delivery are the volume and viscosity of the drug solution loaded, air pressure, and the mouthpiece used. The formulation of solutions used for nebulizers is easy and cheap as compared with that required for pMDIs and DPIs. One of the major disadvantages associated with the use of nebulizers is that they require to be assembled and loaded before each use and disassembled and cleaned again after every use by the patient, which might be difficult for an untrained patient [25].

3 Novel delivery systems targeting respiratory diseases

The potential of pulmonary delivery for the treatment of respiratory diseases has been acknowledged and utilized for more than 3500 years in the form of different technologies. The other routes that are used for lung diseases include oral and parenteral delivery. The concept of repurposing the established drugs for the treatment of respiratory diseases by developing novel pulmonary drug delivery systems has attracted the interest of the biomedical scientific community and the pharmaceutical companies owing to the drug absorption capacity of lungs. Different drug absorption
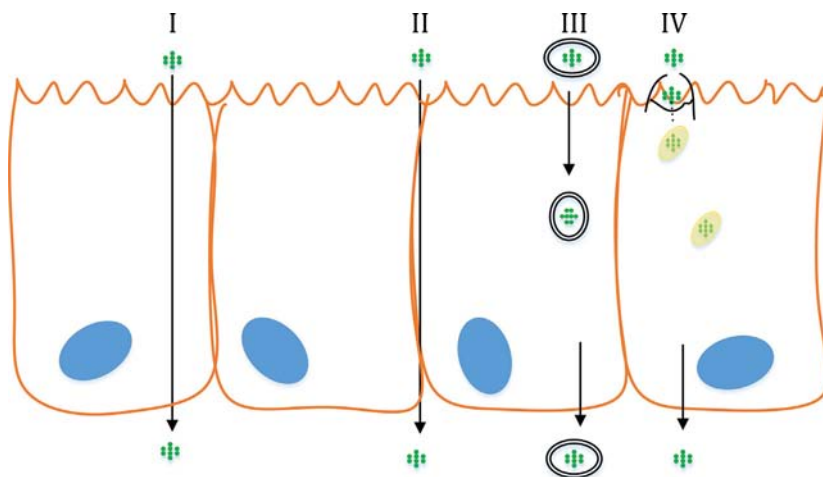
FIG. 2

Drug absorption mechanisms through pulmonary route includes (I) transcellular diffusion, (II) paracellular diffusion, (III) vesicle-based transport, and (IV) carrier-mediated transport.

mechanisms in the case of pulmonary delivery have been discussed in Fig. 2. Several advantages of the pulmonary delivery systems that have intrigued the attention of researchers toward the development of novel pulmonary systems are as follows:

- Lungs have been found to have a high absorptive surface area of about 70–140 m^2 for an adult human covered with a thin layer of mucosa, which allows easy absorption.
- Lungs also exhibit high permeability.
- Peroral and systemic delivery leads to drug delivery throughout the body, thereby a small fraction of drugs reaching the lungs. Targeted delivery using the pulmonary route would enable the delivery of the required amount of drug locally to respiratory tract regions.
- The unwanted systemic side effects caused due to the drug reaching every part of the body can be avoided or reduced.
- Direct delivery to the diseased site would require delivering a lesser drug dose while also providing faster onset of action.
- Several proteins, peptides, or other drugs sensitive to hepatic metabolism or enzymatic degradation can be delivered by pulmonary route in their active state while bypassing drug degradation.
- The reduction in systemic side effects and drug dose can reduce the cost of the treatment in the long run.
- When compared with parenteral administration, pulmonary administration avoids the use of injections, thereby making the treatment more patient compliant.
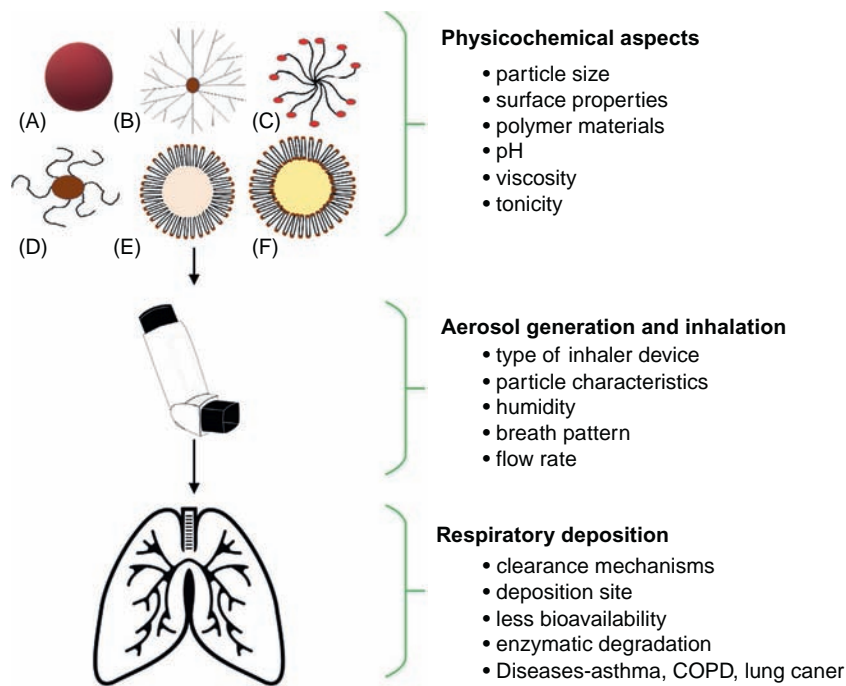- Enhanced therapeutic efficiency.

FIG. 3

Types of particle-based pulmonary systems and the factors influencing pulmonary drug delivery: (A) polymeric nanoparticles, (B) dendrimers, (C) micelles, (D) functionalized nanoparticles, (E) solid lipid nanoparticles, and (F) liposomes.

The development of controlled drug delivery systems for pulmonary delivery has been an area of interest for researchers for long. Many systems have been developed for targeting specific respiratory diseases. The structure of different particle-based pulmonary systems and the factors influencing pulmonary delivery are demonstrated in Fig. 3. However, in spite of increased investigations in this area, not many systems have translated to the market. Some of the most popularly developed systems and their significance for various respiratory diseases would be discussed in this section.

3.1 Nanoparticles

3.1.1 Polymeric nanoparticles

Polymeric nanoparticles can be described as colloidal carriers with diameters ranging from 10 to 1000 nm. The opportunities available for copolymerization, surface modifications, and conjugation of polymers present forward the ability to develop targeted delivery systems, controlled and sustained delivery, and encapsulation of active ingredients. Commonly used polymers for formulation of nanoparticles include both synthetic and natural polymers like chitosan, alginate, albumin, gelatin,

polylactic-*co*-glycolic acid (PLGA), poloxamer, poly(ethylene glycol), and poly(lactic) acid. Polymer-based nanoparticles can be broadly categorized into two types based on the drug encapsulation characteristics. The first type consists of nanocapsules wherein the drug is encapsulated within the polymeric nanocapsules, while the other category is nanospheres, wherein the drug is distributed all over the polymeric matrix. Pulmonary drug delivery through polymeric nanoparticles offers advantages like targeted delivery, escaping the pulmonary clearance, prevention of enzymatic drug degradation, sustained release, enhanced efficacy, and reduced side effects.

Various systems based on polymeric nanoparticles have been evaluated for its applications in the treatment of tuberculosis, infectious pulmonary diseases, fungal diseases, cystic fibrosis, and others. Deacon et al. described the preparation and characterization of tobramycin-loaded alginate/chitosan-based polymeric nanoparticles for treatment and prevention of *Pseudomonas aeruginosa* in cystic fibrosis. The study showed that drug-loaded nanoparticles (NPs) exhibited equivalent antimicrobial activity to that of pure drug. The NPs were further functionalized with dornase alfa, which led to improved penetration of tobramycin-loaded functionalized NPs into cystic fibrosis sputum. The study concluded that antibiotic-loaded functionalized NP therapy can be a good strategy to overcome the mucus barrier in the case of infectious diseases [32].

Another study performed by Derbali et al. also reported the preparation and characterization of antibiotic levofloxacin-loaded polymeric nanoparticles based on poly(lactic acid)-grafted-poly(ethylene glycol) against bacterial infections in cystic fibrosis patients [33]. But these drug-loaded NPs were not further evaluated owing to quick drug release characteristics.

Tuberculosis is another pulmonary infectious disease causing the death of people worldwide. There has been ongoing research to improve the therapeutic efficiency of anti-TB drugs by incorporating them into nanoparticles. Costa-Gouveia et al. reported one such study wherein ethionamide, a second-line anti-TB drug, was loaded in combination with its booster into biodegradable β-cyclodextrin nanoparticles with an aim to improve the efficacy of the drug for the treatment of tuberculosis. The NPs were intended to overcome the issues presented by drug-like crystallization tendency and poor aqueous solubility of the booster. The in vivo study performed on mice wherein in cyclodextrin NPs were administered to mice lungs exhibited a 3-log decrease of pulmonary mycobacterial load [34]. This has been the first study wherein the coencapsulation of drugs has been reported for pulmonary administration targeting tuberculosis treatment. This technology can further be improvised, modified, and evaluated for pulmonary applications.

Despite the advantages offered by polymeric NPs for pulmonary delivery, there are some major limitations associated with these systems that need to be addressed to promote the translation of these systems to the market further. NPs based on natural polymers often tend to degrade quickly, leading to immediate drug release during in vivo administration. To overcome this, NPs based on biodegradable synthetic polymers are being looked at for sustained/prolonged-release inhalation purposes.

Another concern associated with polymeric NPs is the accumulation of these drug carriers onto the airways upon repeated administration. Therefore the toxicity and degradable potential of the polymers used for NPs synthesis must be examined in depth. The stability of the aqueous NP formulations also poses challenges that must be addressed during formulation development.

3.1.2 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) can be defined as colloidal drug carriers with diameter size ranging from 50 nm to 1 μm. They are made up of solid lipids or mixture of different liquid and solid lipids stabilized with the aid of an emulsifier. The lipids generally used for the preparation of SLNs consist of physiological lipids like waxes, fatty acids, triglycerides, and steroids, which are biocompatible and thus can be well tolerated by the body. SLNs exhibit advantages over liposomes like improved stability of drug-loaded nanoparticles due to emulsion-based stabilization. SLNs offer other properties like the controlled release, incorporation of hydrophilic and lipophilic drug, target-based release, easy manufacturing, controllable particle size, easy scale-up, and reduced toxicity. These beneficial properties of SLNs have attracted researchers to evaluate its potential for targeted drug delivery. SLNs exhibit the potential of active targeting by means of surface modification with ligands and passive targeting by enhanced permeation and retention effect owing to their small size. However, for efficient incorporation of hydrophilic molecules, some amphiphilic substances need to be incorporated. SLNs have also found to provide protection to the incorporated drug molecules from physical, chemical, and enzymatic degradations. SLNs also have been found to exhibit enhanced bioavailability, improved pharmacokinetic profiles, and localized drug delivery to diseased sites in the lungs, thereby enhancing therapeutic efficiency and reducing side effects.

The potential of paclitaxel-loaded solid lipid nanoparticles for improved delivery to lung tumors was evaluated by Rosière et al. [35]. It was reported that in vivo pulmonary delivery of coated SLNs exhibited prolonged exposure of paclitaxel in the lungs and reduced systemic delivery, thereby demonstrating that this strategy might enhance the antitumor activity. Another study performed by Ji et al. [36] presented the encapsulation of hydrophobic drug naringenin into solid lipid nanoparticles using emulsification and low-temperature solidification method. The pharmacokinetic study reported that pulmonary instillation of drug-loaded SLNs exhibited significant improvement in the drug bioavailability as compared with that of the pure drug suspension, thereby conforming that SLNs can be used for delivery and enhancing the bioavailability of poorly water-soluble drugs.

Makled et al. [37] evaluated the potential of sildenafil citrate-loaded SLNs for the treatment of pulmonary hypertension by means of targeted delivery via inhalation instead of conventional oral delivery. The drug-loaded SLNs exhibited high encapsulation efficiency, colloidal stability, and sustained-release profile for a period of over 24 h and also remained stable upon nebulization using the jet nebulizer. Thus this SLN-based formulation can further be evaluated for its potential for targeted delivery, reduced dose, and dose frequency along with reduced side effects. SLNs loaded with

rifabutin were encapsulated in microspheres using spray-drying method to enhance their stability and suitability for pulmonary administration in the form of dry powder inhaler in the study performed by Gaspar et al. [38]. In vivo studies performed in mice presented that DPI-based delivery of antibiotic-loaded SLNs to the lungs was efficient, although a relevant amount of drug was recovered from the spleen and liver. A significant decrease in the growth index of *Mycobacterium tuberculosis* was observed in the lungs of mice treated with SLN-loaded microspheres as compared with control, thereby concluding that pulmonary administration of antibiotic-loaded SLNs has promising potential in the treatment of tuberculosis.

Although a large number of research and review papers describing the potential of SLNs for pulmonary delivery are available, very few of these research formulations have actually been translated to the market for availability to patients. Some of the reasons for this gap between research and translation include reduced stability of formulations in a solution state or upon aerosolization/nebulization, off-target delivery, lack of in vivo evaluation supporting data, lack of efficacy evaluation in studies, and safety and compatibility issues. Thus attempts should be made to modify further and evaluate SLN-based systems for their therapeutic potential. Moreover the modifications should be performed, taking into consideration the reason for the failure of previous SLN-based systems in clinical trials.

3.1.3 Inorganic nanoparticles

As the name suggests, this category includes nanoparticles made up of inorganic materials like gold, silver, platinum, and silica, among others. These nanoparticles have been widely investigated for their applications in disease detection, diagnosis, and treatment. The materials used for the preparation of such nanoparticles have been already explored for their application in therapeutics, for example, platinum-based therapeutics used for cancer treatment like cisplatin and carboplatin.

Gold nanoparticles have achieved significant attention of researchers for their applications in biomedical imaging, drug delivery, photothermal therapy, cancer diagnosis and treatment, and others. Gold nanoparticles alone or in combination with therapeutic moieties have also been evaluated widely for their potential in lung cancer therapy. A recent study performed by Ramalingam et al. [39] evaluated the potential of polyvinylpyrrolidone-silver nanoparticles (PVP-AuNPs) conjugated with doxorubicin against human lung cancer cells. The doxorubicin (Dox)-conjugated nanoparticles exhibited pH-responsive drug release wherein lowering the pH led to enhanced detachment of Dox from gold nanoparticle conjugate. Excellent cytotoxic activity exhibited by Dox-conjugated PVP-AuNPs as compared with free drug and pristine nanoparticles implied that conjugation of drug to PVP-AuNPs led to increased concentration of drug in A549 cells, thereby enhancing the cytotoxic effects. Furthermore, Dox-conjugated PVP-AuNPs led to increased production of ROS levels enhancing apoptosis in lung cancer cells while also increasing the expression of tumor suppressor genes. These characteristics exhibited by drug-conjugated PVP-AuNPs could further be evaluated for confirming its potential as a drug delivery system for targeting lung cancer cells.

Aerosol-based delivery of inflammation blocking antibodies to the lungs has been challenged by limitations like active clearance in lungs, reduced residence time, and tissue penetration. To address these shortcomings, various inorganic metal nanoparticles have been evaluated for direct delivery to the lungs in cases of inflammatory diseases. One such study performed by Halwani et al. [40] evaluated the potential of superparamagnetic iron oxide nanoparticles conjugated to anti-IL4Rα blocking antibodies (SPION- anti-IL4Rα NPs) for suppression of inflammation in case of asthma. The optimized SPION- anti-IL4Rα NPs when used for the intrapulmonary treatment of OVA-sensitized mice were found to decrease the levels of proinflammatory cytokines in lung tissues significantly. The NPs also led to decreased proliferation of lung inflammatory cells along with a reduction in the frequency of such proliferation. The SPION- anti-IL4Rα NPs provided better and prolonged control of lung inflammatory cytokines and cells until 7 days' postadministration, thereby efficiently reducing lung inflammation as compared with free anti-IL4Rα. Such systems can further be worked on to modulate them according to clinical needs. Several SPION-based systems have already been approved, and some have reached clinical trials for their diagnostic, imaging, and treatment abilities.

Another inorganic material, calcium phosphate, has been examined as potential delivery system for codelivery of synergistic agents owing to its stable physicochemical properties and biocompatibility. One such study performed by Wu et al. [41] reported the formulation of hollow calcium phosphate nanoparticles coated with phospholipids and its evaluation for codelivery of synergistic drugs paclitaxel and doxorubicin against the lung cancer cells A549. The nanoparticles exhibited a sustained-release profile of the loaded antitumor drugs. Drug-loaded calcium phosphate nanoparticles exhibited high cell inhibition rate, suppressed the tumor proliferation, and promoted the apoptosis of A549 tumor cells. The nanoparticles also exhibited a decrease in tumor volume posttreatment. Based on these in vitro and in vivo results, it was implied that calcium phosphate nanoparticles show promising potential for drug delivery to the lungs, but there exists a need for an extensive evaluation of such systems for translation to clinical use.

Although there has been research going on for the development of inorganic nanoparticle-based delivery systems, not many of them have reached the market, and very few of them have undergone clinical trials. Some of the inorganic nanoparticle products that have been approved by FDA include NanoTherm for glioblastoma; Feraheme, Venofer, INFeD, and Dexferrum for iron deficiency; and Feridex and GastroMARK for imaging. Similar systems modulated according to pulmonary diseases and inhalation route should be focused on in the upcoming research.

3.2 Liposomes

Liposomes can be defined as vesicles consisting of lipid bilayer membrane enclosing an aqueous core. The phospholipids that compose liposomes are amphiphilic lipid molecules wherein the unfavorable interaction of lipophilic parts of lipids with water leads to self-assembly to form spherical bilayer liposomes. Thus the liposomes have

a hydrophilic core and hydrophobic lipid layer membrane, which makes it suitable for encapsulating drugs with various physical properties and drug combinations.

One of the major reasons for the utilization of liposomes for pulmonary delivery is the similarity of liposome composition to that of the lung surfactants comprising 80% of phospholipids and about 8% of neutral lipids. This chemical similarity of liposomes, along with its biocompatible and biodegradable nature, makes it more suitable for pulmonary delivery as the chances of local lung irritation are reduced. Liposomes offer the opportunity for sustained release of drug to a localized area while acting like the drug reservoir. Moreover the phospholipid nature of liposomes allows them to facilitate intracellular delivery to alveolar macrophages. Modifications of the surface of liposomes allow for targeted delivery by means of ligand or antibody binding.

Liposomes have been investigated for local delivery of drugs to the lung for the treatment of diseases like pulmonary infections, cystic fibrosis, asthma, and lung cancer. Treatment of these diseases has posed a challenge since long because most of the therapeutic moieties used for the treatment are hydrophobic in nature, thereby presenting issues in formulation development and delivery. Moreover the deposit of insoluble drugs in the lungs causes drug toxicity even if the drug is delivered locally to the lungs. Liposomes have been investigated for targeted treatment of such pulmonary infectious diseases. Recently a new drug, namely, Arikayce, which is amikacin-loaded liposomal suspension to be delivered by inhalation, has been approved by FDA for treatment of infectious lung diseases caused by a group of bacteria, namely, *Mycobacterium avium* complex. The controlled trials for this formulation exhibited that about 29% of patients administered with Arikayce exhibited no growth of mycobacteria in their sputum cultures for 3 months. The formulation has also been found to be effective against *Mycobacterium abscessus* in patients with cystic fibrosis when administered once a day [13]. This therapeutic ability of inhalable liposomal amikacin formulation is because of its properties like enhanced drug delivery and retention in cystic fibrosis airways, the ability of liposomes to penetrate biofilms, and mucosal layers [42]. Similarly, another inhaled liposomal formulation of ciprofloxacin aimed for the treatment of noncystic fibrosis bronchiectasis (nontuberculosis mycobacterial infections) has cleared phase 2 and phase 3 clinical trials [43, 44]. This formulation, namely, Pulmaquin, has been designated as a Qualified Infectious Disease Product (QIPD) by the FDA recently.

Another respiratory disease wherein the potential of liposomes for delivery and treatment is being evaluated is lung cancer. Generally, late diagnosis of the disease combined with poor treatment options leaves the option of surgical procedures in the end, which is not desirable. Systemic delivery of chemotherapeutics has not been successful owing to the serious associated side effects that are difficult to minimize. Many liposomal formulations consisting of chemotherapeutic drugs like cisplatin and doxorubicin have been developed in research labs, but they have been rejected in clinical trials either owing to toxicity or because they did not exhibit effects better than the already available formulations. For example, several liposomal formulations of cisplatin like lipoplatin, Li-PlaCls, and L-NDDP have reached clinical trials

and exhibit lower toxicity as compared with free cisplatin, but they failed to exhibit enhanced efficacy [45]. Phase I study of aerosolized liposomal cisplatin proved to be safe, but further studies are yet to be performed for applications in lung carcinoma [46]. Similarly, attempts have been made to evaluate liposomal formulations of 9-nitrocamptothecin to overcome its limitations like poor bioavailability owing to poor solubility. Phase 2 clinical trials of liposomal 9-nitrocamptothecin administered by nebulizer indicated that the formulation was safe and feasible for administration to patients with pulmonary malignancies [47].

Liposomal aerosolized formulations have been shown to improve the localized concentration of drugs at the target site, reduced side effects and cytotoxicity, and improved bioavailability in several clinical trials. For these formulations to be translated to market, enhanced drug efficacy profiles compared with the original drugs are required. The successful development of aerosolized liposomal formulation depends on the ability of the liposome formulation and aerosol delivery device to deliver the drug to the target area in the respiratory tracts in required doses while minimizing the side effects.

3.3 Micellar systems

Polymeric micelles can be defined as nanosized colloidal carriers with a core-shell structure. Micelles are generated when amphiphilic polymers are dispersed in aqueous solutions above a threshold concentration known as critical micelle concentration (CMC) and a solution temperature known as critical micelle temperature. The amphiphilic polymers commonly used are composed of block polymers (bi- and tri-), polymer-lipid conjugates, and phospholipids. Self-assembly of amphiphilic polymers in aqueous solutions is guided by the decrease of free energy of the system. At concentrations higher than CMC, the hydrophobic segments of the polymer chain start to associate together, thereby reducing contact with water molecules and forming a core-shell structure with a hydrophobic core. The water molecules then get the opportunity to form hydrogen bonds with the hydrophilic segments of polymer chains, while the contact of hydrophobic molecules with the aqueous region is reduced. Both of these instances lead to a reduction of free energy of the system, thereby leading to the formation of micelles. Repulsions among the hydrophilic regions of micelles prevent the excessive formation of micellar structures. Micelles have been proposed to be used for their ability to encapsulate and deliver poorly water-soluble drugs. Micelles offer advantages like greater physical stability in vitro and in vivo, need-based modification of size, encapsulation efficiency, encapsulation of hydrophilic drugs into the micelle shell, and hydrophobic drugs on micelle core region.

Several micellar systems are being evaluated for their potential in pulmonary drug delivery. The study by Kim et al. [48] presented the formulation and characterization of coencapsulated antiinflammatory drug resveratrol and gene into cholesterol-conjugated polyamidoamine (Chol-PAM)-based polymeric micelles. Resveratrol-loaded Chol-PAM micelles exhibited antiinflammatory effects in the in vitro evaluations. Furthermore, an in vivo study revealed that the delivery of

resveratrol and heme oxygenase-1 gene combination by Chol-PAM micelles through inhalation exhibited the highest antiinflammatory activity for acute lung infections model. Thus the study reported the efficiency of micelles as the carrier for drug and also the suitability of formulation for inhalation-based delivery.

Another study performed by Hu et al. evaluated the pharmacokinetic profile and biodistribution of curcumin acetate and Nile red-loaded PEG-PLGA micelles after intratracheal administration to rats [49]. The in vivo study demonstrated that the intratracheal administration of micelles prolonged the pulmonary retention time as compared with intravenous administration. Moreover the micelles exhibited localized sustained release for up to 24 h. The micelles were also reported to have facilitated the uptake to pulmonary vascular endothelium, thereby paving the way for such systems targeting pulmonary arterial hypertension. The micelles were also found to penetrate the alveolar-blood barrier and reach other organs while maintaining its structure. This property of micelles can be utilized for noninvasive systemic delivery, but this might act as a disadvantage in cases where localized delivery to the lungs is desired.

In another study by Wang et al. [50], paclitaxel-loaded polymeric micelles were developed and evaluated for the treatment of lung tumors by the administration through inhalation. Peptide conjugate Pluronic, in combination with succinylated gelatin, were used for micelle formulation. The unique property of this micellar system was that the release of paclitaxel was triggered by the presence of matrix metalloproteinase 2/9 (MMP 2/9), with the amount of drug released dependent on the concentration of MMP 2/9. The micellar system was found to be stable upon nebulization. The biodistribution study exhibited that the administration of drug-loaded micelles was able to reach similar drug concentrations in the lungs as that by intravenous administration of the system, although the systemic concentrations of drug in case of pulmonary administration was sevenfold less in comparison with that in the case of intravenous administration. Moreover the percentage of drug deposited into rat lungs via inhalation was less than that previously reported for human lungs. The paclitaxel-loaded micelles enhanced the sensitivity of tumor cells to delivered chemotherapeutics while also reducing the toxicity to healthy lung cells. These kinds of environment responsive systems could further be explored while aiming for targeted delivery and reduced side effects, especially in cases of lung cancers.

Despite the advantages offered by polymeric micelle-based systems like environment responsive delivery, reduced side effects, and encapsulation of hydrophobic drugs, several concerns need to be resolved for easier translation and regulatory approval of such systems into the market. The major issue of concern is the dependency of micellar stability on CMC, thereby increasing the chances for the burst release of drugs in case of instability. Moreover the polymers required for micelle preparation are very limited, thereby limiting the use of such systems. Furthermore, the methods for the preparation of micelle systems are difficult to scale up for large-scale production. Keeping in mind the opportunities and the limitations that these polymeric systems offer, attempts should be made to improvise the systems further to fit the clinical need.

3.4 **Microparticles**

Microparticles are the particles with size ranging from 1 to 1000 μm and made up of either natural or synthetic polymers. Generally the particles with a size range of 1–3 μm are used for inhalation delivery using dry powder inhalers. These particles have a density of around 1 g/cm^3, which leads to aggregation and rapid clearance by the macrophages. Thus, to prevent the particles from aggregation and macrophage clearance and assure deposition in the desired area, microparticles with larger size and low density, which are easy to disperse, are proposed. These particles with large size and high porosity exhibit small aerodynamic diameter, which allows them to avoid impaction in the upper tracts and thus the ability to get deposited in deeper regions of the lungs. These microparticles with high porosity are expected to easily escape the clearance by alveolar macrophages, thereby remaining at the site for longer duration and delivering drugs for sustained/prolonged periods.

Several polymers like gelatin, dextran, chitosan, PLGA, and PCL have been evaluated for the formulation and evaluation of microparticles aimed at pulmonary delivery. Among these polymers, PLGA has been the most explored polymer for this kind of application. One of the recent studies conducted by Ubale et al. described the use of PLGA microparticles loaded with antisense oligonucleotide (ASO) against NF-κB for treatment and prevention of lung inflammation [51]. The produced ASO-loaded PLGA microparticles were 2–5 μm in size and exhibited sustained release in vitro over a period of 72 h. The particles were found to be uniformly distributed into the lungs and retained for about 48 h after pulmonary administration in rats. These microparticles were found to control the lung inflammation significantly as compared with the control group by the mechanism of reducing the levels of proinflammatory cytokines like TNF-α and IL-1β. The successful retention of such microparticles in lungs sustained delivery, and reduced inflammation suggests the potential of the use of such systems for targeting inflammatory diseases of lungs. However, there are differences in the inhalation pattern that takes place in rats and humans, which suggests the further need for evaluation of such systems for human use.

Recently, in 2014, Acusphere Inc. received US patent for the development of porous microparticles loaded with the hydrophobic drug for pulmonary administration. Acusphere also has one of its products based on porous microparticles for targeting asthma treatment AI-850 under clinical trials. Porous microparticles have also been proposed for efficient delivery of paclitaxel, an anticancer drug, and also as a contrast agent for ultrasound [52].

Another study performed by Parikh et al. reported the development and evaluation of isoniazid-loaded PCL microparticles and its evaluation for antitubercular activity [53]. The study reported that significantly high levels of isoniazid-loaded microparticles were found in alveolar macrophages when studied in vivo and in vitro owing to phagocytosis of the microparticles. The delivered microparticles lead to an increased level of NO production, which helps improve the efficacy of antitubercular agents without compromising cell viability. Thus it was concluded that such systems could be used to reduce the treatment time of tuberculosis by enhancing the efficacy of antibiotics delivered.

Despite the potential of enhanced efficacy and targeted delivery offered by microparticles, several limitations of these systems hamper their translation into the market and need to be addressed. PLGA-based microparticles, which are the most widely evaluated ones, exhibit limitations like initial burst release of the drug, low drug loading capacity of microparticles, risk of accumulation of PLGA into lungs, and drugs in the core that might be exposed to environmental factors leading to degradation. Porous microparticles expose more area in contact with the surrounding environment, thereby leading to burst release and drug degradation in some cases. The drug loading capacity of the polymeric system is conventionally around 10%. Furthermore the amount of inhalable mass load at a single time ranges from around 25 to 50 mg depending upon the type of inhaler. These factors thus limit the use of polymeric microparticle-based systems for drugs that require low doses to be administered. PLGA degrades into acids, thereby creating an acidic environment that might cause local irritation and also degrade the active ingredients in some cases. Surface modifications to increase drug loading or conjugation could be one of the approaches that can be explored to prevent the burst release. Moreover the modifications require to be specific based on the required delivery rate. Taking into consideration the potential benefits and limitations offered by polymeric microparticles, these systems should be further explored.

3.5 Dendrimers

Dendrimers, also known as dendritic polymers, are branched polymers with well-defined microstructures and polyfunctionality. These polymers differ from the random coil polymers owing to their peculiar structural characteristics. Dendrimers consist of three different components: (a) a core, (b) internal repeating unit layer, and (c) outer functional units. Some of the commonly used dendritic polymers are polyamidoamine (PAMAM), polyester, polyamide, poly (L-lysine), and polyether, among others. Dendrimers exhibit several properties that have attracted the attention of researchers for its application in pulmonary delivery. One of the beneficial characteristics is the ability to choose the suitable size of dendrimers by varying the dendrimer generation; therefore the dendrimer size can be selected based on the desired deposition region in the lungs. Dendrimers provide the opportunity for multifunctionalization owing to the presence of a large number of surface functional groups. Dendrimers have also shown to exhibit improved bioavailability and therapeutic efficiency for loaded drug molecules. Moreover, dendrimers have also shown to improve the physicochemical properties of the loaded therapeutic moieties.

Several dendrimer systems have been assessed for their pulmonary delivery abilities targeting diseases like cystic fibrosis, lung cancer, metastases, chronic asthma, and COPD. Zhong et al. reported the development of PAMAM-conjugated doxorubicin (DOX) nanocarrier systems and evaluated its potential for pulmonary administration and efficiency in the lung metastases model. DOX was conjugated to carboxylated terminals of PAMAM dendrimers by means of the intracellular trigged linker, which would release the drug in a pH-responsive manner (at intracellular

pH 4.5). The conjugated drug-PAMAM nanocarrier exhibited a significant decrease in the tumor burden and significant in the animal survival rate when compared with that of free DOX administered through intravenous and pulmonary route. Moreover, biodistribution studies revealed an enhanced localization of drug in the lungs and reduced distribution to heart as compared with the free drug [54].

Another study performed by the same group evaluated the effects of surface modification of dendrimers with PEG on the biodistribution and pharmacokinetic profile of dendrimers after systemic and pulmonary administration [55]. In this study, amine-terminated PAMAM dendrimers were conjugated with PEG on the surface and evaluated further. It was found from the pharmacokinetic profiles that both PEGylated and non-PEGylated dendrimers reached their peak concentration within a few hours of administration via the pharyngeal aspiration route, thereby negating the effect of chemistry on peak plasma concentration. Therefore it was found through the study that a high density of surface modifications with PEG and the administration route affects the biodistribution and the pharmacokinetic profiles. Pulmonary delivery of unmodified PAMAM dendrimers led to the concentration of about 83% of delivered dendrimers in the lungs, while only 2% of dendrimers reached lungs after intravenous delivery. The PEGylated dendrimers also were reported to be readily internalized by lung endothelial cells (20%) as compared with that of unmodified ones. Contrary to this, about 35% of unmodified dendrimers were taken up by lung epithelial cells, whereas only 24% of PEGylated dendrimers were uptaken. This study therefore suggests that suitable surface modification of dendrimers can be performed to manipulate the biodistribution, pharmacokinetic profiles, and targeted delivery to desired organs. Moreover the chemistry of dendrimers also affects the cell uptake, thereby suggesting suitable modifications in cases where specific cells require to be targeted.

One of the novel strategies being worked upon to treat inflammatory lung diseases like asthma, COPD, barotrauma, inflammation, and reduced function caused after lung transplantation has been targeted delivery of RNA to lung endothelial cells. One such study performed by Khan et al. described the use of a combination of PAMAM and poly(propylene imine) (PPE) dendrimers with lipid substitution for encapsulation and delivery of siRNA [56]. The study showed that siRNA encapsulated in chemically modified dendrimers exhibited higher avidity toward lung endothelial cells. Among all different combinations evaluated, PAMAM-conjugated with C_{15} lipid tails, PPE dendrimers with C_{15}, and C_{14} lipid chains were found to exhibit high potency dependent on diameter for optimal delivery to endothelial cells. Moreover, factors like the chemistry of modified dendrimers and pK_a values of nanoparticles were suggested to have an impact on the targeting window of dendrimers. Such systems can further be explored for targeted delivery of therapeutics like mRNA, DNA, and microRNA.

The aforementioned studies therefore lead to the conclusion that the dendrimer chemistry plays an important role in determining the behavior of dendrimers upon in vivo delivery. Therefore the chemistry of dendrimers, along with drug conjugation or encapsulation, can be exploited to achieve desired delivery characteristics.

Moreover the route of administration also has a pivotal role to play. Despite the many advantages offered by dendrimer-based pulmonary delivery, toxicity caused by these positively charged dendrimers still remains a challenge. The positively charged dendrimer systems are known to react with negatively charged biological membranes, thereby causing potential cytotoxicity and hemolytic toxicity. Attempts have been made to reduce this toxic potential of dendrimers by masking the cationic charge by means of conjugation with hydrophilic polymers and PEG. Moreover the production of such dendrimer-based delivery systems at a large scale with required clinical standards still poses challenges required to be addressed.

3.6 Gene therapy

Gene therapy, by means of viral and nonviral vectors, has also been evaluated for aerosolized administration targeting diseases like cystic fibrosis, lung cancer, alpha-1 antitrypsin deficiency, and asthma. Viral vectors have been found to be highly efficient in gene transfection, but they incite the formation of antibodies. Thus the nonviral vectors were developed and evaluated, which mainly consists of cationic polymers. These nonviral vectors are more efficient in binding to airway epithelium but less efficient in gene transfection as compared with that of viral vectors. Aerosolized gene therapy has been evaluated for tumor suppressing agents, epidermal growth factor suppressing agents, immunosuppressing agents and others. Various cationic polymers like polyethyleneimine (PEI), PEI/PEG complex, and amphiphilic block polymers have been explored to form nanocomplexes for gene delivery [57].

Therapeutic proteins and peptides, which are often classified as biopharmaceuticals, have proved their potential for the treatment of various autoimmune diseases, diabetes, cancer, and others. Peptides and protein therapeutics exhibit high selectivity and efficacy as compared with small molecule drugs, which have led to increased demand for development of delivery methods for such therapeutics. The physicochemical properties of such therapeutics like high molecular weight and hydrophilic nature limit their applications for disease treatment. Protein/peptide therapeutics face difficulty in crossing the biological membranes due to their physicochemical nature, thereby resulting in low bioavailability. One of the ways to overcome such limitations has been the evaluation of pulmonary delivery of proteins and peptides for local and systemic applications.

A recent study published by Patel et al. reported the formulation of inhalable in vitro transcribed mRNA nanoformulation for protein production in the lungs. Herein cationic polymer poly(beta-amino esters) (PBAE) was used owing to its ionizable and biodegradable nature for the delivery of mRNA through nebulization. The strategy of hyperbranching was utilized to modulate the properties of the polymer in accordance with the requirements for inhalable systems while maintaining its chemical backbone preserved, which could be identified for efficient gene delivery. In vivo, pulmonary administration in rats exhibited a uniform distribution of luciferase mRNA throughout the lungs and the production of luciferase protein. It was also found that a single nebulized dose of hyperbranched PBAE polyplexes with mRNA

transfects about 24.6% of lung epithelial cell population. Thus repeated dosing of this inhalable formulation was found to produce proteins consistently without causing local or systemic toxicity. This system can be used to deliver mRNAs to the lungs for the treatment of diseases like cystic fibrosis and others [58]. It can be observed here that the polymer was chosen based on its ability to degrade at the site and the chemical backbone required for gene delivery, further modified to make it suitable for pulmonary delivery. This kind of approach can be further evaluated with different polymers to develop suitable systems required to meet the clinical need.

Many systems have been evaluated for gene therapy, but very few of them have cleared the clinical trials and reached the market. One of the reasons behind the low translation of such systems into the market despite good results in animal studies has been safety and effectiveness in human disease models. Further investigations regarding the same needs to be performed to meet clinical needs.

3.7 Immune therapy/vaccines

Chemotherapeutic agents like antibiotic and antiviral agents are the standard treatment modes for respiratory tract infections like cystic fibrosis, pneumonia, rhinosinusitis, chronic obstructive pulmonary disorder. However, there has been a decline in the effectiveness of these agents for the management of respiratory tract infections owing to pathogen resistance. Therefore many alternate treatment strategies are being worked upon with immunotherapeutics being one of the widely studied. Immune therapy consists of therapeutic antibodies and proteins that are delivered in the form of prophylactic for disease prevention and therapeutics for disease management through parenteral routes. However, preclinical studies have revealed that the parenteral route might not be the best route to administer the high-molecular weight immunotherapeutics due to their incapability to reach lungs efficiently [59]. Thus investigation of inhalation-based systems through oral and intranasal routes are being studied so as to overcome the barriers put forward by the parenteral routes. Immunotherapeutic delivery by pulmonary route has been studied for targeting local diseases in the lungs and for systemic delivery owing to high absorption property through the alveolar surface area [60].

Aerosolized dornase alfa, which is a recombinant human deoxyribonuclease, is one of the earliest aerosolized therapy directed for cystic fibrosis treatment. Pulmozyme is the marketed formulation of therapeutic protein dornase alfa, which has been found to reduce the sputum viscoelasticity when administered in case of cystic fibrosis [61]. But this has been the only aerosolized nucleotide-based formulation to date.

FluMist Quadrivalent is a marketed nasal inhalation-based vaccine containing live attenuated influenza virus, which is sprayed into the nose to protect against influenza [62]. Another live attenuated vaccine Nasovac (Serum Institute of India Ltd.) is an intranasal vaccine against influenza A (H1N1) virus [63].

Most of the intranasal vaccines introduced or studied are liquid in nature, thus making the incorporated immunotherapeutics susceptible to thermal degradation,

formulation instability, and chemical instability, thus leading to degradation of the active therapeutic agent and loss of efficacy and potency. To overcome this challenge the formulation of vaccines in the form of dry powder inhalers could be the approach for further research. Many studies have evaluated the stability of dry powder vaccines at varying temperatures and humidity and found them to be stable and as efficacious as liquid vaccines when reconstituted. However, dry powder vaccines would be required to have protection against humidity [64].

4 Marketed pulmonary drug delivery systems
4.1 Marketed devices for respiratory diseases

There are several nanoparticle/microparticle-based pulmonary inhalation systems that have been approved by the FDA and entered the market for their applications in imaging, diagnostics, and treatment of respiratory diseases. Despite a large number of pulmonary systems that have been researched on, very few of them make their way to clinical trials, and even fewer manage to pass through the trial and reach the market. The reasons for this are the complex preparation procedures for the nanoparticle-based systems, stability issues for the formulation, safety concerns associated with the biodegradability and biocompatibility of developed systems, chemical instability of encapsulated active ingredient, large-scale production, and economical nonfeasibility of the systems. Table 1 enlists the pulmonary delivery systems that have reached the market for the treatment of respiratory diseases and for systemic delivery. It can be observed that most of the systems that have been translated into the market are liposome-based pulmonary inhalation systems.

Despite the plethora of research in nanoparticle-based delivery in the last five decades, very few of them have translated clinically. One of the major challenges arises when the functionality of nanoparticle systems is complexed to develop systems for targeted delivery, stimuli sensitive, or multifunctional. Multiple chemical synthesis steps are required to integrate multiple functionalities into the nanocarrier-based systems, which again becomes challenging for production at large scale wherein good manufacturing practices are required to be followed at each step. This results in increased production cost and increased evaluation criteria for the formulation of quality control [65]. Another factor that plays a role is the intellectual property (IP) rights associated with the developed systems. Many factors like targeted or nontargeted delivery, types of drugs that can be loaded, and intended application for the system affect the IP strategies, and thus any of these factors might contribute to weakening the IP, thereby adversely affecting the research and development of such products [66]. Moreover the clinical trials for nanomedicines are more complex as compared with that of conventional delivery systems owing to a large number of control groups required to assess the effects of various nanoparticle components on the cells and tissues.

Different types of inhaler devices are available in the market to assist the aerosol delivery to lungs for the treatment of respiratory diseases. Table 2 enlists some of the

Table 1 List of pulmonary delivery systems launched in the market.

Sr. no	Device/ formulation name	Company	Indication	Description	Drug
1.	ARIKAYCE	Insmed	*Mycobacterium avium* complex (MAC) lung disease	Liposomal suspension for inhalation administered using Lamira nebulizer system	Amikacin
2.	TOBI PODHALER	Novartis	Cystic fibrosis with *Pseudomonas aeruginosa*	Dry powder formulation consisting of tobramycin enclosed in hypromellose capsule	Tobramycin
3.	Curosurf	Chiesi USA	Respiratory distress syndrome in premature infants	Liposomal nanoparticles intended for enhanced delivery and reduced side effects upon intratracheal instillation	Poractant alfa
4.	Apulmiq	Aradigm	Noncystic fibrosis bronchiectasis	Inhalable formulation consisting of free ciprofloxacin and ciprofloxacin loaded liposomes (cleared phase 3 trials)	Ciprofloxacin
5.	Afrezza	MannKind Corporation	Diabetes mellitus	Inhalable recombinant insulin with excipients that self-assembles to form microspheres in the acidic environment	Insulin
6.	Alveofact	Boehringer Ingelheim Pharma	Respiratory distress syndrome in premature infants	Liposomal suspension consisting of surfactant	Fat extracted from lung lavage fluid
7.	Survanta	Abbott	Respiratory distress syndrome in premature infants	Liposomal formulation consisting of surfactant	Beractant
8.	Paclitaxel-based DPI	InhaTarget	Lung cancer	Drug-loaded nanocarriers (micelles and SLNs) for targeted delivery to lungs, enhanced residence time (under development)	Paclitaxel
9.	Cisplatin-based DPI	InhaTarget	Lung cancer	Cisplatin dry powder for inhalation, noninvasive delivery (preclinical stage)	Cisplatin
10.	Pulmosphere	Novartis	Respiratory diseases	Phospholipid containing formulation with drug suspension, solution or drug-loaded porous microparticles	N/A

Table 2 Inhaler delivery systems available in the market.

Sr. no	Name	Type	Company	Description	Drug	References
1.	ELLIPTA	DPI	GlaxoSmithKline	Single- or two-strip, single-step activation, multidose inhaler, can be used unassisted by patients above 7 years of age; requires low inspiratory rate	Fluticasone furoate	[67]
2.	Pulmicort Flexhaler	DPI	AstraZeneca	Multiple-dose inhaler, driven by inspiratory flow, used for treatment of asthma in patients above 6 years of age	Budesonide	[68]
3.	PROAIR RESPICLICK	DPI	Teva Pharmaceuticals	Multidose breath-actuated inhaler used for acute asthma symptoms, bronchospasm	Albuterol sulfate	[69]
4.	Diskus/ Accuhaler	DPI	GlaxoSmithKline	Multidose inhaler with consistent dosing across varying flow rates. It consists of defined doses in laminated strips	Salbutamol/salmeterol/ fluticasone propionate/ salmeterol + fluticasone propionate	[70]
5.	AKITA Jet	Jet nebulizer	Vectura	Smart jet or mesh nebulizer. Individualized delivery of drug dose based on the patient's lung function information. Indicated for severe uncontrolled asthma (leading phase 3 trials)	Budesonide	[71]
6.	ProAir HFA	pMDI	Teva Pharmaceutical Industries	pMDI inhaler with inbuilt dose counter used for prevention or treatment of bronchospasm in asthma or COPD for patients aged 4 years or older	Albuterol sulfate	[72]

Table 2 Inhaler delivery systems available in the market—cont'd

Sr. no	Name	Type	Company	Description	Drug	References
7.	Ventolin HFA	pMDI	GlaxoSmithKline	pMDI inhaler with inbuilt dose counter used for prevention or treatment of bronchospasm in asthma or COPD for patients aged 4 years or older	Salbutamol	[72]
8.	I-Neb	Mesh nebulizer	Philips	Battery powered mesh nebulizer comprising of adaptive aerosol delivery system. Optimal drug delivery, reduced nebulization time	N/A	[73]
9.	Respimat Soft Mist	Liquid inhaler	Boehringer Ingelheim Limited	Multidose inhaler that produces soft mist, propellant-free, handheld liquid inhaler. Indicated for patients with COPD and obstructive respiratory diseases	Tiotropium bromide monohydrate	[74]
10.	Staccato	Breath-actuated inhaler	Alexza Pharmaceuticals Inc.	Single breath activation system wherein rapid vaporization of drug occurs to form aerosol particles for inhalation delivery	N/A	[75]
11.	PARI eFlow	Rapid nebulizer	PARI International	Vibrating mesh nebulizer with easier handling and reduced time of nebulization	Tobramycin	[76]
12.	Conix	DPI	3M Drug Delivery Systems	Passive DPI that utilizes the high energy and shear forces of vortex to deagglomerate the particles. Unique feature is that only fine API particles are inhaled while large lactose particles are retained in the chamber	Fluticasone propionate Salmeterol xinafoate	[77]

aerosol delivery technologies that are clinically utilized. The systems generally comprise dry powder inhalers, pressured metered-dose inhalers, different types of nebulizers, and the advancements in these systems. The most commonly used type of inhaler devices used for pulmonary delivery is the pMDIs. They have been widely used for decades by patients suffering from diseases like COPD and asthma in the form of a single drug or combination of drugs. One of the major challenges associated with the use of pMDIs is the correct use of the device by the patients. To address this issue the new pMDIs have been developed with breath-actuated technology, wherein the drug is emitted from the device after it senses the patient's breath, thus solving the coordination problems with actuation and breathing. Another major development in the pMDI technology has been the shift from the use of chlorofluorocarbon (CFC)-based propellers to hydrofluoroalkane-based propellers for pMDIs [78]. Newer technologies like Respimat Soft Mist have been introduced, which is a combination of properties of pMDI and nebulizers that do not require a power supply and aerosolizes the drug solution in the form of soft mists. This combined technology was found to exhibit a significant reduction in the oropharyngeal deposition of the aerosol [79].

DPIs are another commonly marketed and clinically used inhaler devices that do not have coordination issues regarding patient breathing and device actuation. The DPIs are more stable chemically as compared with aerosolized suspension or solution because of low reactivity in powder form. Different types of DPIs are available, which can be classified as single-unit dose disposable, single-unit dose reusable, multiunit dose, and multidose reservoir. They can also be classified into passive and active DPIs. The main issue with passive DPIs is the variability in the inspiratory forces among patients of different ages and health conditions, thereby affecting dose uniformity. Active DPIs have internal energy sources added to them so that the dose uniformity is not dependent on the patient's inspiratory flow rate [80].

Staccato is another breath-actuated inhaler device that vaporizes the drug film using heat, which is later condensed into the form of small droplets into the lungs and is intended for systemic application [81].

Nebulizers are another type of inhaler device available in different varieties and have recently gained attention due to the higher costs of hydrofluoroalkane (HFA as propellant)-based inhaler devices. The nebulizers with advanced technologies include the breath-actuated, breath-enhanced, mesh, and vibrating nebulizers. Breath-actuated nebulizers release aerosolized formulation only when it senses that the patient is breathing. This coordinated release avoids wastage of drug during exhalation and avoids environmental exposure to toxic drugs. On the other hand a breath-enhanced nebulizer is designed such that it entertains the airflow during inspiration and vents out the expired air outside the device, thereby increasing the output rate and decreasing the administration time. Vibrating mesh nebulizers have a mesh plate attached to them, which vibrates upon the action of the piezoelectric element and breaks the aerosol droplets into fine particles before delivery, thereby increasing the aerosol deposition in the alveoli [82]. There have been newer technologies that sense the breathing pattern of patients and releases drug only when appropriate breathing is detected, for example, AKITA [83].

4.2 Patented novel pulmonary systems

As discussed in the previous sections, there have been many technological advancements in the field of pulmonary delivery devices and technologies like nebulizers, pMDIs, DPIs, and others to make the delivery more efficient and patient compliant. Despite numerous efforts, there still exist many unmet clinical needs in the area of pulmonary delivery that needs to be addressed and has been widely being worked upon by the researchers. Table 3 enlists the recently patented novel pulmonary delivery systems utilizing the concept of nano/micro-based drug delivery.

Some of the issues that need attention from the researchers have been discussed here. One of the most important factors is the consistency and reproducibility of the generated aerosols for pulmonary drug delivery. We need technologies that could assure the generation of consistent aerosols, thereby delivering an accurate amount of drug each time to every patient. Delivering large doses is also a crucial factor that poses challenges in the case of pulmonary delivery. A small fraction of the drug is deposited into the lungs when delivered through most of the inhaler systems, which might not be enough dose for treatment of some diseases, thereby creating the requirement for repeated delivery, thus reducing patient compatibility and causing discomfort. Moreover the choice of the inhaler, the comfort level of the patient to use the inhaler, inhaler technique, and adherence to inhaler regimen are some of the other concerns that require to be focused on while developing newer inhalation technologies.

The newly patented technologies consist of nanoparticle-based technologies for targeting respiratory diseases via pulmonary delivery. The patents include a wide range of polymeric nanoparticles, lipid nanoparticles, liposomes, micelles, dendrimers, and others. These novel systems are intended to have advantages like enhanced efficiency of delivery, enhanced therapeutic efficiency, controlled delivery, targeted delivery, an alternative to invasive delivery, and reduced side effects, as can be analyzed from the recent patents described in Table 3. Despite the high number of advanced patented technologies, very few of them are actually translated to market because the developed systems turn out to be unsafe, causing side effects, not significantly more efficient than the already existing systems, along with issues in large-scale production and translation. There is a need to boost this translation of newer technologies from lab to land.

5 Future prospects and conclusions

The pulmonary route has been found to be promising for the delivery of drugs locally to lungs and rapid systemic delivery for several diseases. The pulmonary delivery offers advantages like the rapid onset of delivery, self-administrable noninvasive delivery, enhanced efficiency, localized action, and reduced side effects. The inherent properties offered by lungs such as high surface area and low enzymatic environment further make pulmonary delivery even more desirable. However, there are several challenges that are required to be tackled for successful pulmonary delivery,

Table 3 Recently patented delivery systems intended at pulmonary delivery

Patent number	Year	Description of the invention	Disease targeted	Remarks	References
US20190169224	2019	Intranasal composition consisting of nanocrystals of hydrophobic agents such as triamcinolone or fluticasone	Asthma, COPD	Proposed for treating or alleviating a respiratory disease	[84]
US10034837	2018	Polymeric nanoparticles or polymeric nanoparticles encapsulated within cross-linked polymeric microparticles of chitosan or chitosan-derived polymers	Chronic obstructive pulmonary disease (COPD), bronchial asthma, cystic fibrosis (CF), chlorine inhalation, influenza myocardial infarction (MI)	Nitric oxide- and nitrite donor-loaded polymeric nanoparticles are proposed to be delivered through DPI	[85]
WO2018031771A1	2018	Therapeutic drug-loaded polymeric nanoparticles with a coating of mucoadhesive polymer (PLGA nanoparticles with chitosan coating)	Allergic asthma, COPD	Increased therapeutic effects, prolonged residence time of NPs at site, targeted delivery	[86]
US10004764	2018	Red blood cell membrane-derived microparticles (RBC MPs) expressing phosphatidylserine on their surface delivered to lungs via inhalation	COPD, asthma, bronchiolitis, acute lung injury, lung allograft rejection (acute or chronic), pulmonary fibrosis	Enhanced production of immunoregulatory cytokines, reduced inflammation, reduced injury	[87]
US2018005580	2018	Aerodynamically light drug particles (levodopa) in combination with sugar or salt	Parkinson's disease	On-demand rapid delivery of drug	[88]
US20180161404	2018	Polymeric nanoparticle (PLGA) for controlled delivery of surfactant protein D to lungs	COPD, bronchitis, lung infections, hypoplasia, CF, influenza	Controlled delivery of protein	[89]

Table 3   Recently patented delivery systems intended at pulmonary delivery—cont'd

Patent number	Year	Description of the invention	Disease targeted	Remarks	References
US9545401	2017	Aerosol formulation consisting of ciprofloxacin encapsulated in liposomes	Respiratory tract infections, cystic fibrosis		[90]
US20170042818	2017	Gel microparticles wherein each microparticle consists of multiple drug-loaded nanoparticles	Nonsmall cell lung cancer	Fine-tuning of drug-loaded nanoparticles from microparticle matrix, active targeting, enhanced efficacy	[91]
US9421166	2016	Dispersible powder consisting of aminoglycoside with phospholipids as the carrier	Bronchiectasis, cystic fibrosis, localized respiratory infections	Reduced side effects due to localized delivery of antibiotics, reduced potential of antibiotic resistance	[92]
US20160113995	2016	Lipid nanoparticle of polymyxin	Respiratory tract infections (*P. aeruginosa*)	Polymyxin-loaded lipid nanoparticles (fatty acids and mono-, bi-, and triglycerides)	[93]
US9072664	2015	Surface-modified inorganic nanoparticles suspended in dryable liquid carriers	For drug delivery in case of respiratory diseases	Improved flowability of particles for DPIs	[94]
US20150224062	2015	Nanostructured aggregates consisting of immunosuppressive drugs (tacrolimus and cyclosporine) for delivery through pulmonary route	Pulmonary fibrosis, bronchiolar asthma, graft rejection	Rapid dissolution of nanoparticles in lungs, avoidance of hepatic first-pass metabolism, increased the local concentration	[95]
US20140294939	2014	Liposomes loaded with mRNA encoding the desired protein administered via the pulmonary route	Treatment of deficiencies of proteins and enzymes	Enhanced stability, the systemic release of proteins	[96]
US20130136688	2013	Aerosol consisting of polymeric nanoparticle with noncovalently anchored linker on one side and one coupling group (maleimide) on another portion	Treatment and diagnosis of lung cancer or bronchial dysplasia.	Potential for targeted delivery to desired tissue/cells by varying the linker and coupling group	[97]

US8574623	2013	Liposome carrier for delivery of therapeutic agent (siRNA)	Pulmonary fibrosis	Specific delivery to extracellular matrix producing cells in the lungs	[98]
US8574623	2013	Liposome carrier for delivery of therapeutic agent (siRNA)	Pulmonary fibrosis	Specific delivery to extracellular matrix producing cells in the lungs	[98]
US20100260853	2010	Compositions consisting of polypeptide/antibody domain with droplet size less than $5 \mu m$	COPD, asthma	Proposed for diagnostic, prophylactic or therapeutic purposes	[99]
US20080213373	2008	Dry powder consisting of drug-loaded nanoparticle aggregates or microparticles (capreomycin and leucine)	Tuberculosis, severe acute respiratory syndrome, Respiratory syncytial virus	Improved delivery, needleless delivery	[100]
US7182961	2007	Drug-loaded particulate composition with a particle tap density of less than $0.4 g/cm^3$ and a geometric diameter greater than $5 \mu m$	Airway diseases	Aerodynamically light particles, highly dispersible particles, optimal particles for aerosols	[101]
US6706892	2004	Particulate formulations consisting of active ingredients with the ability to form covalent bonds with blood/pulmonary proteins	Treating inflammation, bronchodilation	Enhancing the drug stability and blood absorption of the agents	[102]

which includes rapid drug degradation, clearance mechanism by the alveolar macrophages, limited control over the particle deposition, and site of deposition of inhaled formulations.

Several particle-based systems (nanoparticle/microparticle) have been found to be promising for optimized pulmonary delivery to lungs for targeting respiratory diseases that utilize the advantages offered by lungs while addressing the limitations offered by physiological barriers at the same time. Several such systems like polymeric nanoparticles, solid lipid nanoparticles, liposomes, micelles, and dendrimers that have been developed for pulmonary delivery have been discussed in brief. Particle properties of the different systems like particle size, surface properties, composition, shape, and others affect the delivery characteristics of the system. These properties of the nanoparticle-based systems are modified to achieve characteristics like the desired release rate, site of deposition, targeted release, and protection of the active ingredient. Various patents and marketed nanotechnology-based pulmonary systems have been discussed while indicating the novel feature that has introduced into the systems from an improvement perspective.

Despite great advancements in the development of nanoparticle-based pulmonary delivery systems, the clinical translation of such systems for targeting respiratory diseases remains a challenge. The physical properties and behavior of the inhaled particles are quite different than that characterized in vitro. These differences exhibited in the in vitro and in vivo behavior is often the reason that many nanoparticle-based delivery systems fail to perform significantly more efficient than the existing systems in the clinical trials. Therefore this factor should be taken into account while developing newer nanomedicines. Moreover, complexity of formulation procedure, formulation stability, batch-to-batch variability, economic burden, efficiency, and safety are some of the factors that require to be taken care of at the laboratory stage itself while developing newer systems. The systems further require to be specialized with respect to the specific requirements of the respiratory disease required to be targeted. After the development of a stable delivery system targeting lung diseases, another concern is its delivery in the form of aerosols through the inhaler devices. Delivery of the drug-loaded particles to the desired site of action through inhalation requires the use of appropriate inhaler that does not affect the formulation stability negatively while generating reproducible aerosols. Patient compliance and ease of use of the inhaler device correctly also play a crucial role. Modifications and advancements in the design of inhaler devices have been one of the strategies to enhance the drug bioavailability at site and residence time of the drug in the lungs.

The computational fluid dynamics modeling approach has provided new opportunities for the researchers to understand the dynamics of aerosol transport, dispersion, and deposition in the alveoli throughout the lungs. These kinds of studies can help to modulate the formulation parameters of inhalation-based pulmonary delivery systems [103, 104]. Moreover, modeling strategies like in vitro, ex vivo, and in silico modeling have been introduced to study the transport and deposition of particles from inhaler-based systems to different regions of the respiratory tract and the significant factors affecting them. These systems can further be used for studying the

mucociliary clearance of particle-based systems and penetration kinetics. Moreover the effect of factors like particle size, shape, charge, surface chemistry, functionalization, and others can be further evaluated to aid the design and development of newer, more efficient pulmonary delivery systems. These models also could be used for personalizing the delivery strategy and device design as per the patient's disease condition.

As discussed previously in the chapter, for the treatment of any respiratory tract infections, the pulmonary delivery system is required to deposit a minimum therapeutic dose to the diseased site to achieve the desired therapeutic effect with minimum side effects. Thus, along with the understanding of the deposition mechanism and the factors affecting it, studies are also required to understand the correlation between drug deposition and its pharmacokinetic behavior postdelivery. To achieve this, physiologically based pharmacokinetic modeling has been introduced to study the local concentration after deposition, predicted response, and toxicological assessment. This kind of modeling approach to understand and analyze the system better would help in the successful development of new pulmonary delivery systems and new therapeutics.

Novel pulmonary delivery technologies have made significant contributions to improve the efficiency of delivery and targeted delivery to lungs for respiratory diseases. An increase in the number of FDA-approved nanoparticulate delivery systems for various diagnostic and therapeutic purposes has led to an increase in the research and development of such systems. An adequate understanding of the lungs' physiology and clearance mechanism can further aid in the development of novel and more efficient nanoparticulate pulmonary delivery systems with higher levels of safety and efficacy. Thus extensive research is still required to eliminate the gaps between laboratory and industrial production of formulations to ensure the translation of more advanced PDDS into the market to fight against the prevailing respiratory diseases.

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