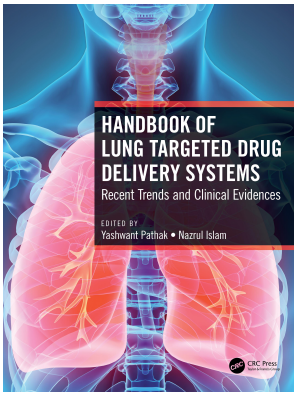

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

Yashwant Pathak, Nazrul Islam

Introduction to Lung Physiology from a Drug Delivery Perspective

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Aparoop Das, Manash Pratim Pathak, Pompy Patowary, Sanghita Das
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Introduction to Lung Physiology from a Drug Delivery Perspective

Aparoop Das[1,#], Manash Pratim Pathak[1,2], Pompy Patowary[1,3], and Sanghita Das[3,4]
[1]Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, India
[2]Pratiksha Institute of Pharmaceutical Sciences, Assam, India
[3]Division of Pharmaceutical Technology, Defence Research Laboratory, Assam, India
[4]Pharmaceutical & Fine Chemical Division, Department of Chemical Technology, University of Calcutta, Kolkata, India

1.1 Introduction

1.1.1 Brief Introduction to Nanotechnology and Nanoparticle Mediated Drug Delivery

Nanoparticles (NPs) are nanosized materials used to embed drugs, imaging agents and genes intended for targeted drug delivery by covalent conjugation or noncovalent attachment (1). As defined by the International Organization for Standardization, NPs are those having at least one dimension less than 100 nm. The American Food and Drug Administration (FDA) has cited another broader definition of NPs as 'engineered to exhibit properties or phenomena attributable to dimensions up to 1000 nm', which is typically adopted in academic research (2). To deliver the appropriate amount of the desired drug precisely to the target organ without causing any side effects while also taking care of the induction of drug resistance is a daunting task; however, it is an important requirement in a targeted drug delivery system (DDS) (3). NP drug carriers can modulate drug distribution via passive and active targeting. Passive targeting is the process by which nanoscaled particles accumulate in tumors/sites of inflammation merely due to their size, whereas active targeting works through the attachment of biochemical moieties which facilitate delivery to diseased tissues expressing biomarkers distinguishing them from the surrounding healthy tissue (4). The term *nanotechnology* involves manipulating and controlling nanoscale (1–100 nm) objects. For over 28 years, the potential benefit of nanotechnology has been appreciated by most researchers and has revolutionized the field of drug delivery and drug targeting with the hope of transforming Ehrlich's hypothetical concept of a "magic bullet" into clinical reality.

The new interdisciplinary platform of nanotechnology-based DDS shows a great deal of promise with several advantages such as improved solubility and bioavailability of hydrophobic drugs, rendering them suitable for parenteral administration encapsulation efficacy which enhances the drug release profiles, high drug payload, extended drug half-life, improved therapeutic index of peptides, oligonucleotides, etc., controlled release along with reduced immunogenicity, and toxicity (5). They can further be used for drug delivery to the central nervous system (CNS) owing to their smaller size and higher barrier permeability.

1.1.2 The Inhalation Route

Drug delivery via the inhalation route has been known since the distant past, when the Egyptians inhaled black henbane vapour to treat various diseases (6). The lung is taken into high consideration as an attractive target among a myriad of routes of administration due to its several advantages (2) over conventional oral administration. Drug delivery to the lungs by inhalation offers a targeted drug therapy for a wide range of respiratory diseases including lung cancer, chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis (CF), tuberculosis (TB), pneumonia and pulmonary hypertension (7), among which COPD, lower respiratory infections and lung cancer are the third, fourth and sixth causes of death worldwide respectively. Other than pulmonary disease, inhaled medications are also beneficial for treatment of anxiety, hypertensive crisis, certain seizures, arrhythmias, spasms, nausea and myriad forms of pain (8).

The inhalation route has received widespread attention within the drug delivery field as it possesses many characteristics ideal for drug transportation and has many advantages over other methods, since the lungs have a large surface area (100 m²) and a very thin epithelial layer (0·2–0·7 μm) for high blood perfusion, elevated blood flow (5 L/min), extensive vascularization to promote systemic delivery, high solute permeability, avoidance of first pass metabolism, and sustained release of the drug and thus reduced dosing frequency (9–11). In addition, drug-metabolizing enzymes are present in much lower concentrations in the lungs than the gastrointestinal tract and liver, thereby limiting enzymatic and proteolytic interaction with the inhaled molecules (8). Moreover, the lung is capable of absorbing

First Author and Primary Contact

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pharmaceuticals either for local deposition or for systemic delivery by targeting the drug delivery carriers to the alveolar region with uniform distribution. Additionally, in inhalation drug delivery there is no risk of needle injuries and health-care staff are not needed, resulting in better patient compliance. The pulmonary tissue has notably high levels of systemic bioavailability for macromolecules, making it the best non-invasive absorption route. Although drug molecules are absorbed more efficiently from the lung than from any other non-invasive routes, however, the therapeutic efficacy of inhaled drugs is limited by their rapid clearance in the lungs (12).

The practice of respiratory medicine has entered into a brave new era through the development of new therapeutic strategies and improvement of current therapies, with some NPs already developed into commercial products. Although inhalation devices and aerosols containing various drugs have been used since the early 19th century, currently there are three main delivery devices used for pulmonary delivery of drugs, viz. nebulizers, pressurized metered-dose inhalers and dry powder inhalers (DPIs) to deliver solutions, suspensions and dry particles respectively (13, 14) and an array of carrier systems, which hold great potential for treating diseases that require direct lung delivery. An ideal delivery device has to generate an aerosol in the range of 0.5–5 μm and provide reproducible drug dosing without affecting the physical and chemical stability of the drug formulation (15). Moreover, the ideal inhalation system must be a simple, convenient, inexpensive and portable device. Although efficient and reproducible pulmonary deposition of aerosol medicines is now possible with current technology, however, the mechanism of the action of particles after pulmonary deposition is highly complex due to the various barriers and clearance mechanisms in the respiratory tract, which pose significant challenges in formulation development (6). The fate of particle–lung interactions are still being researched and have become indispensable for pharmaceutical scientists to develop more effective inhalable formulations. Moreover, toxicity and regulatory concerns limit approval of nanotechnology-based medicinal products (16).

The primary focus of this chapter is to provide an insight into the physiological and efficacy aspects of the mechanism of pulmonary DDS with respect to the lung structure and characteristics, and also the research progress on various parameters to be considered during formulation development and how molecular properties affect rate and extent of pulmonary drug absorption, clearance and metabolic mechanisms, etc. Herein, we have also highlighted the future opportunities for nanotechnology focusing on the treatment of lung diseases.

1.2 Anatomy and Physiology of Lungs

A. Anatomy of lungs/gross tissue organization:
   i. The respiratory system:

Energy is produced in the form of adenosine triphosphate (ATP) in the body through cellular respiration. For cellular respiration, cells need oxygen (O_2) as a reactant, and carbon dioxide (CO_2) is produced as a waste product. As excessive CO_2 may become toxic, it is eliminated from the body by the joint cooperation of the respiratory and cardiovascular systems. However, intake of O_2 and expulsion of CO_2 is performed solely by the respiratory system, and the cardiovascular system supports the entire system by aiding in the transportation of blood containing the gases between the body cells and lungs. Apart from the regular gas exchange, the respiratory system also participates in a repertoire of functions like blood pH regulation, aiding in smelling, and production of the voice, and it helps the body gets rid of heat and water in exhaled air (17, 18).

Structurally, the respiratory system consists of two main parts: (a) upper respiratory system and (b) lower respiratory system. The nose, nasal cavity, and pharynx and its associated structures comprise the upper respiratory system and the larynx, trachea, bronchi and bronchioles comprise the lower respiratory system (17). Functionally, also, the respiratory system is divided into two parts, i.e. the conducting zone and the respiratory zone. The conducting zone is not directly involved in gas exchange which includesthe nose, nasal cavity, pharynx, larynx, trachea, bronchi, bronchioles and terminal bronchioles. These components filter, moisten or warm the air and facilitate conduction of the air. The respiratory zone is the site where gaseous exchange takes place and this zone includes respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli, and here the gaseous exchange takes place between air and blood (18).

   ii Upper respiratory system:
      a. Nose and nasal cavity:

The nose is the external and visible component of the respiratory system and is followed by the internal component inside the skull called the nasal cavity or internal nose. The nose is made up of bone and hyaline cartilage which is covered by muscle and skin and is lined by mucous-secreting cells called goblet cells. The nasal cavity is a two-way irregular passage for the entry of air and is divided by a septum. The posterior part of the septum is made up of ethmoid bone and vomer, and anteriorly made up of hyaline cartilage. The nasal cavity is lined up with the vascular ciliated columnar epithelium containing goblet cells that secretes mucous which coats the nasal hairs and make them sticky. Bones in the face and cranium that are filled with air are called paranasal sinuses and are present in the nasal cavity. Some of the sinuses are maxillary sinuses in the lateral wall, frontal and sphenoidal sinuses in the roof and ethmoidal sinuses in the upper portion of the lateral wall of the nasal cavity (17, 19).

Inspired air passes through the nose, which is the first respiratory passage, and then the air enters the nasal cavity where air is filtered, moistened or humidified, and warmed. Sticky hairs in the nares of the nasal cavity filter the air from any particles or microbes from the external environment. As the filtered air passes through the mucosa, which are in moist condition, the air becomes moistened. There is a huge vascularity surrounding the mucosa that makes the passing air warm inside the nasal cavity. Other than the regular respiratory functions, the nose and nasal cavity perform some non-respiratory functions like aiding in olfactory stimuli and modifying voice through speech vibrations.

b. Pharynx and its associated structures:

The pharynx is the continuation of the nasal cavity and is a tube-like structure formed of skeletal muscle which is lined by mucous membrane. The associated structures of the pharynx are basically its three major regions, namely the nasopharynx, the oropharynx and the laryngopharynx.

The nasopharynx is the superior portion of the pharynx that is posterior to the nasal cavity and extends up to the soft palate. It acts only as an airway and houses the pharyngeal tonsils in its top. Auditory tubes (or eustachian tubes), which connect to the middle ear cavity, directly open into the nasopharynx. The oropharynx is the intermediate part of the pharynx. The position of the oropharynx lies posterior to the oral cavity and extends towards the hyoid bone from the soft palate. It acts as the passageway for both air and food. There is a distinct change observed in the epithelium lining where the pseudostratified ciliated columnar epithelium changes to stratified squamous epithelium during the transformation of nasopharynx to oropharynx. Finally, the laryngopharynx forms the inferior portion of the pharynx, posterior to the larynx, which begins from the level of the hyoid bone. It continues as the passageway for air and ingested material where the respiratory and the digestive systems move away from its inferior part. Finally, the laryngopharynx ends in the larynx and enters the esophagus (18).

iii Lower respiratory system:

a. Larynx

The larynx or "voice box" is the connecting point between the laryngopharynx and the trachea. The size of the larynx differs slightly in males and females. It is usually larger in males than females, which is why males have a larger "Adam's apple" and deeper voices. The Adam's apple, or thyroid cartilage, is made up of two hyaline cartilages that are fused to form the anterior wall of the larynx, which makes its shape triangular. The thyroid cartilage (anterior), epiglottis (superior) and cricoid cartilage (inferior) make up the structure of the larynx.

The epiglottis is a leaf-shaped fibro-elastic cartilage attached to the thyroid cartilage and covers the opening of the trachea. It lies obliquely behind the tongue and behind the hyoid bone, and forms a lid over the 'glottis. The epiglottis is lined up by squamous epithelium. It closes the larynx during the swallowing of food materials and thus protects the lower airway passage from food particles.

The vocal cords are stretched across the opening of the larynx and are made up of non-keratinized stratified squamous epithelium, goblet cells and basal cells. Tension in the vocal cords produced by the surrounding muscles determines the pitch of the voice. Vocal cords produce low-pitched sounds when the muscles around the vocal cords are relaxed followed by opening of the vocal cords; this phenomenon is called *abducted* (open). When the surrounding muscles contracts, the vocal cords are stretched out and produce a high-pitched voice; this phenomenon is called *adducted* (closed) (19).

b. Trachea:

The trachea or windpipe is the continuation of the larynx, located anterior to the esophagus and divide into left and right primary bronchi at a junction known as the *carina*. The layers of the wall of trachea, starting from superficial to deep are (1) adventia, (2) hyaline cartilage, (3) submucosa, and (4) mucosa. The function of the trachea is quite similar to the nasal cavity, i.e. same protection against dust with the help of a mucous membrane lining consisting of ciliated pseudostratified columnar epithelium.

c. Bronchi and bronchioles:

Bronchi are separated to left and right at the carina. The carina is surrounded by nervous tissue that detects foreign particles and induces coughing to expel them. Cartilage rings give mechanical support to the bronchioles and prevent them from collapse. Pseudostratified ciliated columnar epithelium lines up the bronchus that contains goblet cells that produces mucus. Bronchi act as a passageway for air and trap foreign particles in and out of the lungs. Bronchioles, which are 1 mm in diameter, start from the tertiary bronchi and branch further to terminal bronchioles that facilitates gaseous exchange through the alveolr sacs.

d. Alveoli:

With the respiratory bronchioles begins the respiratory zone. When respiratory bronchioles reach deeper, the epithelial lining changes from simple cuboidal to simple squamous epithelium. The respiratory bronchioles are further subdivided into alveolar ducts and the terminal parts are called alveolar sacs, which are analogous to a cluster of grapes. Alveoli basically participate in the gas exchange. Two types of cells are found in the lining of the alveoli: type I alveolar cells and type II alveolar cells. Ninety-seven percent of the alveolar surface area is made up of type I alveolar cells which are the main site for gaseous exchange. Type II alveolar cells secrete alveolar fluids that help in maintaining moisture between the cells and the air, thus reducing the surface tension of the alveoli. The alveolar wall is surrounded by alveolar macrophages that phagocytes foreign particles and pathogens that reach the alveoli (17, 18).

B. Particle deposition:

The deposition of particles in the lungs takes place four different ways (20). They are interception, impaction, sedimentation and diffusion.

i. Interception: When a particle travels very close to the epithelial surface, the particle tends to be intercepted; however, the size and length of the particle determines the interception. Fibres having the dimension of 1 micrometer (μm) and length of 200 μm suffer interception.
ii. Impaction: Suspended particles in air tend to travel in their own pathways; however, when there is a band along the path, the particle tends to stick or impact on

the surface of their path. This type of impaction depends on the velocity of the air and mass of the particle. Particles greater than 10 μm are deposited in the nose or throat and are unable to reach the lower respiratory system.

iii. Sedimentation: This type of deposition happens in the case of particles having size greater than 0.5 μm and takes place in the bronchi and bronchioles. When particle size is very small, the buoyancy of the particle is overcome by gravitational force and air resistance, and as a result, the particle is deposited on the surface.

iv. Diffusion: This type of deposition happens in the case of particles of sizes smaller than 0.5 μm and takes place in small airways and alveoli. Particles with such smaller sizes act like gas molecules and follow the *Brownian motion*. Due to the smaller size of the particles, their movement is vigorous and they are deposited mostly in the lower respiratory region; however, the may also deposit in the upper respiratory region.

C. Pulmonary surfactant:

Pulmonary surfactant lines the surface of the alveoli, lowering surface tension and preventing atelectasis (complete or partial collapse of the entire lung or some area of the lung) during breathing. Surfactant consists of a phospholipid, dipalmitoylphosphatidylcholine, and four surfactant-associated proteins, SP-A, SP-B, SP-C, and SP-D. Out of the four, SP-A and SP-D are hydrophilic and participate in the pulmonary host defence. SP-B and SP-C are hydrophobic and assist in reducing the surface tension of the surfactant. The cuboidal type-II cells in the epithelium produce pulmonary surfactant. Initially, a thin layer of any inhaled drug will be deposited in the pulmonary surfactant, followed by deposition and absorption in other respiratory regions (21, 22). The surface tension reducing property of the surfactant prevents the drug particle from forming drug droplet aggregation, and so, when designing a inhaled drug formulation, care should be taken to select drugs or associated compositions that do not disturb or damage the pulmonary surfactant.

D. Mechanism of drug absorption and clearance:

Study of pulmonary absorption and elimination is still in the nascent stage. The complex structure of the lungs and the presence of surfactant have made the study difficult. Soluble macromolecules are absorbed from the lungs to the body essentially by two mechanisms: absorptive transcytosis (passage through the cells) or transcellular transport and paracellular transport (passage between the cells).

Absorptive transcytosis may be independent of any receptor or transporters, like passive diffusion, and may involve receptor or transporter mediated binding to facilitate absorption. For a drug molecule to be absorbed, following passive diffusion, from the lung epithelial lining into the blood, the drug has to pass through various barriers such as the surfactant, epithelium, basement membrane and the vascular endothelium. However, the process of absorption may become more complex if the drug follows active transport and utilizes receptors or transporters (transport molecules). Transporters are surface molecules that facilitate the movement of drug molecules inside (influx transporter) or outside (efflux transporter) of the cell through the ATP dependent mechanism. Most of the drugs, mostly hydrophobic, are absorbed through passive diffusion. There are mainly two different families of transporters. They are the solute carrier transporters superfamily (SLC) and ABC. OCT1, OCT2 and OCT3 are some significant transporters belonging to the SLC family, and P-gp, MRP1, MRP2, MRP3, MRP4, MRP5 belong to the ABC family.

When transportation of molecules takes place in the junctional complex between two cells, then it is called paracellular transport. Paracellular transport may also occur between three cells when there is a specific spot on the circumference between endothelial and epithelial cells. In another type of paracellular transport, a large "pore" is formed in the basement membrane as a result of the death of a cell. This pore is eventually filled up by new cells and these new cells seal the monolayer in the basement membrane. Small hydrophilic and small peptide molecules can be absorbed by paracellular transport. Sometimes, absorption enhancers like chitosan may disrupt the tight paracellular junction, which may result in intercellular transport of the drug (23, 24).

Drugs are cleared from the respiratory system mainly by mucociliary clearance, enzymatic degradation and clearance by alveolar macrophage. All these clearance types depend upon the size, chemical nature and site of deposition of the drug particles.

i. Mucociliary clearance:

Mucociliary clearance is instrumental in removal of foreign particles like inhaled pollutants and pathogens as well as secretions. The mucociliary apparatus is made up of cilia, a gel-sol layer consisting of a *gel* phase that contains mucins and other glycoproteins overlaying the watery *sol* phase or periciliary fluid where cilia can beat without resistance. The mucus is produced by goblet cells in the epithelium and the submucosal glands. The ciliated cells transport the mucus containing the foreign particles in a proximal direction to get the mucus swallowed or expectorated. Particles larger than 6 μm in diameter are eliminated from the airways by mucociliary clearance; however, smaller particles penetrate the mucus and escape the mucociliary clearance (23, 25).

ii. Enzymatic degradation:

Similar to the liver, some metabolizing enzymes like CYP2S, CYP2F and CYP4B1 from the cytochrome P450 family are also found in the lungs. Some phase-II enzymes like UDP UGT, SULT, GST, estrase and peptidase are also reported to be expressed to some extent in the lungs. Apart from the cytochrome P450 enzymes, proteases also play an important role in the stability and pharmacokinetics of inhaled drugs and may

contribute to the pathology of many respiratory diseases. Increased enzyme concentration in the lungs due to diseased condition plays as a barrier for delivery of drugs to treat respiratory diseases (26).

iii. Clearance by alveolar macrophage:

Any drug that tends to dissolve slowly is eliminated by the alveolar macrophages by means of phagocytosis. Macrophages transport the insoluble drug to the mucociliary escalator along the alveolar surface or translocate to the tracheobronchial lymph, or may be disposed of by enzymatic degradation internally. Phagocytosis is size dependent, and is optimal for particles having sizes of 1.5–3 μm (23, 25). So the particle size should be kept in mind to avoid clearance by the alveolar macrophages. Many engineered particles have successfully avoided alveolar clearance by increasing the porosity or by PEGylation (27, 28).

1.3 Nanoparticle-based Systems for Pulmonary Application

Nano-based drug delivery technology gains new horizons as unfavourable physical properties of the particles have been modified, including enhancing drug solubility and encapsulation efficiency, and improving the drug release profile in order to obtain better pharmacokinetic and therapeutic efficacy. In the 1990s, conventional colloidal carriers like emulsions, liposomes and polymeric nanoparticles were replaced by solid lipid nanoparticles (SLN), aqueous nanoscale suspensions made up of phospholipids and triglycerides because of the advantages such as improved stability at room as well as body temperature, lipophilic and hydrophilic drugs can be loaded, targeted drug delivery, higher drug content capacity, water-based technology, easy to sterilize, biodegradable and biocompatible (5, 29–31). SLN provide affordable and patient-friendly drug delivery through various routes, and hydrophilic SLN has shown promising effects for various ailments such as cancer and tuberculosis (32). Most importantly, SLN compositions exhibit physiological resemblance that allow them to exert the least toxic effects and make them ideal for pulmonary drug delivery. Benefits from administration of SLN encapsulated drugs through pulmonary routes include controlled release characteristics and rapid degradation. Also, SLN exerts physiological tolerability and can be drug targeted to pulmonary macrophages which makes SLN a useful tool in treating lung infections (33). Some core lung regions exhibit the predominant appearance of phospholipids which play a pivotal role in maintaining essential respiratory mechanisms, e.g. alveolar phospholipid-based surfactant proteins essential in regulating optimal surface tension and decreasing friction in the lung tissue (32, 34). Drug delivery through the pulmonary route opens up new horizons for drug administration to the lungs directly and is one of the most important non-invasive techniques because of its higher bioavailability as lower proteolytic activity and a highly vascularized, thin epithelial barrier, as well as a large alveolar surface area, enables more efficient drug absorption, reduced dosing frequency, and includes very few side effects along with bypassing first pass metabolism and the appropriate size desired for pulmonary delivery promotes transepithelial transport by avoiding alveolar macrophage clearance (32, 35, 36). Nebulization of SLN has gained increased interest in current research as it has been observed that aerosolized drugs showed quick absorption because of the large surface area of the alveoli and the presence of thin walls of the alveolar airspaces, leading to augmented blood flow and permitting entry to systemic circulation (31, 32). SLN can be chosen as a carrier to improve bioavailability of drugs in treating lung cancer, where nebulization of SLN of antitubercular drugs reduced the dosing frequency and also imparted improved drug bioavailability in the treatment of pulmonary tuberculosis. Other studies revealed that biodistribution of radio-labelled SLN has shown significant uptake of the radio-labelled SLN into the lymphatics after inhalation (37).

A. Solid lipid microparticles (SLM)

Solid lipid microparticles (SLM) are the least exploited particulate delivery system, as their suitability in comparison to submicron-sized particles are limited. Despite being the least popular, the main interest about lipid microparticles (LM) is due to their simpler production by high pressure homogenization, lucid characterization techniques, increase in size leading to extended release properties (38, 39) and reduced dose of microparticles as loading capacity is much higher. Solid lipid microparticles (SLN) are almost same as they have the same composition, with biocompatible lipid and solid particle matrixes and characteristic control release properties. Differences observed among SLN and SLM are in the size ranges, as SLN has a submicron size of 50–1000 nm and SLM is 1–50 μm. Interestingly, LMs display higher physicochemical stability than LNs. Lyophilization can be performed for LMs without any changing of particle characteristics, but aggregation of LNs occurs if lyophilization is carried out without cryoprotectors (40). Reduced surface area makes LM take up less surfactant than LNs to stabilize as maximizing surfactant ratios is prone to exhibit adverse effects (41). Particles in a dry powder inhaler tends to aggregate in lungs and undergo macrophagic clearance rapidly with geometric sizes between 1 and 3 μm and mass density near 1 g/cm^3 (42). Particle size is an important parameter as particles of <1 μm are easily exhaled before reaching the target and those smaller than 1–0.5 μm are deposited in the alveolar region where particles of >5 μm are deposited at the oropharynx and upper respiratory tract, and for appropriate lung deposition through inhalation drug delivery, particles should have an aerodynamic size range of 1–6 μm. SLM can be a suitable option for targeting drug in lungs through pulmonary delivery as anatomically the lungs curb the efficiency of inhaled aerosols depending on the particle size. ,The optimized particle size of 1–5 μm has been considered to reach and retain in the targeted airway region for stipulated period of time to exert the desired effect as SLMs of 1–50 μm in sizes express excellent flow properties and large geometric size helps in avoiding phagocytosis by

macrophages in lung and attains the sustained release of formulations attainable (31). Some research on SLM has evidenced the promising drug delivery of quercetin to exert anti-oxidant and anti-inflammatory properties for treating ailments like asthma (43).

B. Polymers

Polymers are covalently bonded macromolecules and can be used for better delivery, and a drug's effects can be extended as it attaches to drugs by an encapsulation technique. A polymeric drug delivery system enables delivery of drug to the site of action with improved safety and efficacy due to benefits that include improved surface area; higher, non-degradable encapsulation efficiency of the drug; prolonged drug delivery and a long shelf life. The putative role of polymers is to encapsulate nanoparticles, microparticles and large porous particles (LLPs) for fabricating formulations. Natural (albumin, chitosan, hyaluronic acid, etc.) as well as synthetic (poly-lactic-co-glycolic acid, poly-lactic acid, polyethylene glycol) polymers are most commonly used for drug delivery systems. Therapeutically poly (lactic acid) (PLA), poly (lactic-*co*-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), alginate, chitosan and gelatine bases are used frequently (44). Polymer selection for encapsulation of drugs in nano, micro, or other polymeric forms needs great attention in order to make a formulation with all the essential characteristics, such as size, charge, biocompatibility, rate of drug release, dosing frequency, drug accumulation in the site of action and rate of polymer degradation. (45). Polymers can act in a controlled release manner, which is of utmost importance in pulmonary drug delivery. Mechanisms behind the drug release behaviors of polymers are drug diffusion, polymer swelling and polymer degradation (46). Poly lactic-co-glycolic acid (PLGA) describes a broad category of drug encapsulation and is the mostly explored polymer for pulmonary drug delivery in a sustained release manner (47). Biocompatibility and biodegradability properties of PLGA exerted nontoxic potential in several in vitrostudies of human airway cell lines, and safety profiling was confirmed by in vivo pulmonary drug drlivery in mice model (48). PLGA is used in pulmonary drug delivery, and it has been noticed that various natural and synthetic polymers affect the viability of cells and hampered bioaccumulation potential. Augmented lung inflammation, more non-viable cells, neutrophil infiltration and hemorrhagic conditions were noted upon use of PLA and PLGA polymers formulation, and these studies showed that PLGA exerts higher cytotoxic effects than sodium hyaluronate and chitosan (49). Besides this, because of their mucoadhesive property, chitosan encapsulated PLGA nanoparticles have shown higher residence time in the lungs (50). The chitosan based PLGA encapsulated palmitic acid-conjugated exendin-4 antidiabetic nano drugs showed to be released in 3 days and hypoglycemia was induced in vivo in mice within 4 days. Thease outcomes suggested the discontinuation of the use of chitosan for pulmonary delivery as it might cause edema in lungs because of the widening of pulmonary epithelial junctions (51).

C. Liposomes

Liposomes can be described as one or more spherical concentric lipid bilayers separated by aqueous buffer compartments (52). Lipid based drug delivery systems adopting sustained release properties making them release over longer periods of time with maximum drug effects are a very tempting option for pulmonary delivery as the basic material is phospholipids, which are intrinsically present in lungs. Other than microparticles, among nanoparticle-based advanced drug delivery strategies, liposomes hold an advantage as an enormous amount of the molecules, proteins and peptides can be incorporated in liposomes, and a very attractive thing about liposomes in pulmonary delivery is that they have reached the clinical development stage (53) and carry advantages like the ability to solubilize poorly soluble drugs, the capacity to provide a reservoir for sustained release, the ability to prolong local and systemic therapeutic levels, their facilitation of intracellular delivery of drugs, especially to alveolar macrophages, the avoidance of local irritation of lung tissue, the ability to target specific cell populations using surface-bound ligands or antibodies, and the potential to be absorbed across the epithelium intact to reach systemic circulation (54).

Classification of liposomes depends on their size and morphology into multilamellar vesicles (MLVs; 0.1–20 μm), large unilamellar vesicles (LUVs; 0.1–1 μm) and small unilamellar vesicles (SUVs; 25–100 nm) (55). Approximately 20% of human pulmonary surfactants in lung tissue by dry weight constitute lipids, and others are phospholipids, which are chemically the same so liposome composition makes liposome an ideal choice for pulmonary drug delivery. Certain parameters like particle size, which is a critical factor in depositing drug into deep lungs should be taken into account in developing inhalable liposome particles. Stability assessment of liposomes in bronchoalveolar lavage fluid depends on the increased transition temperature of the lipid mixture, which is determined by an important variable — rigidity — as heat produced during nebulization promulgates impact on the leakage of liposome encapsulated drugs because the temperature is higher than the phase transition temperature (Tc) of the lipid mixture (56). In the case of inhalational liposomal dry powder formulations, leakage of encapsulated drug occurs during lyophilization and jet milling. Therapeutically, liposomes were shown to be efficiently effective in treating pulmonary diseases, In pulmonary tuberculosis the use of liposomes provides an improved strategy for delivery of antitubercular drugs in lungs. Citing lack of effectiveness from broad spectrum antibiotics in oral and IV routes, Conley et al. reported treatment of *Francisellatularensis* infection in mice using ciprofloxacin encapsulated liposomes administered through jet nebulization (57). In this area of research, liposomes have been suggested as surfactant replacement

therapy in patients with respiratory distress syndrome. Respiratory distress syndrome in neonates has recently been prevented using lung surfactants based on mixtures of phospholipids, e.g. Survanta (58). Many studies have also shown that drugs entrapped in liposomes are safe for pulmonary delivery since liposomal drugs work in a controlled release manner, which means doses causing huge adverse effects can be reduced to produce a therapeutic effect. Liposomal drug delivery systems have been shown to modify the delivery of chemotherapeutic agents in the management of lung cancer and prophylaxis of metastasis when compared to the IV route of administration. An example of a chemotherapeutic agent, cisplatin, used in lung cancer treatments has several disadvantages, like dose-limiting toxicity (DLT) in systemic administration, followed by nephrotoxicity, peripheral neuropathy and ototoxicity, but clinical Phase I trials showed pharmacokinetics, safety and efficacy with aerosolized liposomal cisplatin at maximum tolerated doses in metastatic lung carcinoma (59).

1.4 Treatment of Chronic Diseases Through the Pulmonary Route

A. Tuberculosis (TB)

Since the 1950s, the choice of drug delivery through the pulmonary route has gained interest as the occurrence of pulmonary tuberculosis (TB) arises from the portal entry of a pathogen, such as mycobacterium, that causes TB (60). In pulmonary delivery the absorption of drugs into systemic circulation takes place from the large surface of the lung mucosa and maintains high drug concentration in lung tissue along with bypassing the hepatic first pass effect (61). In pulmonary TB management, advantages of pulmonary delivery lie in the fact that lungs play a pivotal role as, starting from site of drug absorption, drug delivery to the primary site of action takes place in the lung. Also, phagocytosis of substances like macromolecular drugs, particulates or vesicular drug delivery in lungs are carried out by alveolar macrophages (AM) that house TB bacilli. It also makes possible the delivery of such agents that may change the rationality of host–pathogen (62). Possibly available aerosol delivery methods in treating TB are advanced technologies, along with conventional nebulization, that have been in clinical practice for a long time (63–65). The readily available and known measures for delivering medicaments to pulmonary regions like the lungs and airways are pressurized, metered-dose inhalers (pMDI) or metered dose inhalers (MDI). MDIs act by regulating the optimized dose to be administered at the site of action by using a dose-metering valve and propellant aerosols (66, 67). Delivery of a drug under positive pressure can be done by nebulization using dry powder inhalers (DPI), which depend on the indrawn breath of the patient to pull in a dry powder (68). Intratracheal delivery of drugs has been a choice of pulmonary delivery in in vivo animal experiments in treating TB. The most widely used aerosolized strategy for drug delivery of liquid or dry powders through the lungs in animal models is accomplished with the PennCentury Micro Sprayer, which quantifies the amount delivered accurately as it ignores the nose and throat and is directly inserted at the bronchial bifurcation down the trachea of the unconscious animal (62). Moreover, distribution studies of formulations can be achieved using dyes or fluorescent dyes. Despite the conventional oral or injectables routes, drug delivery through inhalational enables administration of anti-TB agents in the lungs. Sukhanov et al. described the advantages of resolving lung lesions in human patients by the administration of cycloferonact as an immunomodulator through the inhalation route for 5 weeks (69). Also, delivery of surfactants through inhalation can be achieved for TB therapies. Efficacy of treatment through inhalational drug delivery in infected animal lungs has been studied elsewhere. Aerosol formulations of a variety of drugs, including rifampicin, rifabutin, rifapentine, isoniazid, ethambutol, ethionamide and capreomycin have been investigated to treat TB and found to reduce bacterial contamination in lungs (62).

B. Lung cancer

About 1.3 million annually reported cases of cancer and deaths all over the world result from a highly prevalent ailment: lung cancer (70). Treatment of lung cancer by pulmonary drug delivery has gained notice as the disadvantages of other routes of administration can be avoided. Oral and intravenous (IV) injection routes face the difficulty of maintaining optimum concentration of chemotherapeutic drugs, as very low concentrations can reach the lung (71, 72). The inhalational route of drug delivery has received much attention in recent days as human insulin powder of recombinant DNA for inhalational delivery has been approved, for example, Exubera® (later withdrawn by Pfizer citing poor acceptance by patients and clinicians) and Afrezza® (manufactured by MannKind Corporation, Danbury, CT, USA, and approved by the US Food and Drug Administration in 2014). Micro- and nanosized particles encapsulating chemotherapeutic drugs have been investigated for delivery to the lungs through the inhalational route (73). Gill et al. prepared micelles made up of polyethylene glycol $(PEG)_{5000}$–distearoylphosphatidylethanolamine (PEG_{5000}–DSPE) caryingpaclitaxel showed well, maintaining paclitaxel concentrations in lungs for long durations after intra-tracheal delivery (74). Small lipid nanoparticles of paclitaxel delivered by inhalation were found to be more efficient in reducing hyperplasia and hypertrophy in comparison to IV delivery. A study also explored and reported the benefits of DOX-conjugated dendrimer in lung cancer therapy through pulmonary delivery (73).

C. Diabetes

Diabetes is a chronic metabolic disorder characterized by inadequate insulin secretion with an increase in

glucose level (75). Since 1920, insulins have been in use for treating diabetes via various routes of delivery such as oral insulin, implantable peritoneal insulin pumps, subcutaneous insulin, etc. In 1924, pulmonary insulin delivery was first examined (76, 77) and inhaled insulin treated individuals with type 2 diabetes mellitus as an adjuvant therapy. Most excitingly, it has been seen that a patient's compliance with and acceptance of inhaled insulin is greater than for subcutaneous insulin (78). Inhalation of insulin showed a decrease in the blood glucose level (77, 79). The efficiency of insulin inhalation depends on the breathing activity, as slow inhalation facilitates the best penetration to the alveolar spaces and attains target, where rapid inhalation leads to inappropriate or loss of drug concentration in the target site of the lung (80, 81). Some examples of inhaled insulin systems extensively studied in clinical protocols are Exubera, a drug approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for type 1 diabetes mellitus and type 2 diabetes mellitus therapy, which was developed in 2006 as a collaboration between Nektar Therapeutics and Pfizer. The device delivers dry powder formulation packed in blister packets containing 1 mg or 3 mg of regular human insulin. Aradigm Corporation and Novo Nordisk together developed the AERx insulin diabetes management system (AERx® iDMS), which delivers insulin in aerosol droplets along with an electronic control device that helps the patient to inhale the insulin in a reproducible pattern. The Technosphere system introduced a placebo formulation of dry powder recombinant human insulin microspheres for patients with type 2 diabetes mellitus. This system was developed by Mannkind Corp. with the MedTone inhaler (Pharmaceutical Discovery Corp.) and this system currently has reached phase III clinical trials (82).

D. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a chronic vascular disorder characterized by elevated levels of pulmonary vascular resistance (PVR) resulting from imbalanced pulmonary vascular remodeling. Vasodilation of pulmonary arteries and blood circulation serves as the lifesaving cure in the pathological condition of PAH (83). Despite other modes of therapy and routes of administration, inhaled vasodilators find their way to provide effective and specific pulmonary vasodilation without hampering systemic pressure (84–88). Advantages of inhalation therapy regarding PAH treatment open up new horizons for treating such conditions as it ranges from the local delivery of drugs and exerts enhanced efficacy as a higher concentration of drugs is retained at the site of action. Interestingly, pulmonary delivery minimizes drug concentration in systemic circulation, which in turn lowers the chances of having systemic adverse effects like systemic hypotension caused by the vasodilation activity of medicaments. This delivery system offers effective therapy in a cost-effective way along with minimizing frequency and drug dose as well as achieving the rapid onset of action and drug absorption (57–60).

Although the development of drug delivery systems is just emerging, these systems show a promising future. Lungs offer a vast variety of advantages over conventional oral drug delivery, making pulmonary drug delivery rapidly gain importance. The enormous gas-exchange surface of the lungs represents a versatile, highly promising and little-exploited route for drug delivery in the treatment of chronic diseases. Furthermore, such a route for drug administration may also be manipulated for systemic drug delivery. The interaction of inhaled particles with the lung has been dynamically developed and has been the subject of intense research in recent years. In this chapter, we have reviewed efficient pulmonary drug delivery systems by understanding the characteristic features of pulmonary drug transport, the deposition mechanics, the nature of therapeutic agents, properties of delivery systems, the molecular basis of pulmonary diseases and barriers to drug delivery. Pulmonary drug delivery of nanoparticles is a non-invasive method that can be designed to target specific cells or organs while sustaining the release of the therapeutics locally or systemically. However, the future of pulmonary drug delivery research requires more reasonable regulation and better understanding of the properties of nanoparticles in achieving different biological effects along with development of more safety excipients and better manufacturing technologies. Moreover, international standards of guidelines of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) need to be defined for in vitro and in vivo models in order to allow valid comparisons between studies and to define the safety and efficacy of proposed treatments.

Again, the ligand-based carrier system for pulmonary targeting should be evaluated for stability and effectiveness to overcome regulatory restrictions. Addressing the toxicity of inhaled therapeutic nanocarriers is matter of inescapable importance. Scientists and researchers have given many and varied answers in an attempt to address all the rising issues, find alternatives and engineer adequate systems to fulfill requirements and needs. Because of the high degree of heterogeneity and complexity in diseased lungs, there is still a large, underdeveloped area of research regarding how inhaled nanomedicines will act under these circumstances. With the growing global trend to look for more precise medicines and diagnosis, application of nanotechnology to biologic therapeutics for developing the next generation delivery devices for better management of pulmonary disease/disorders looks bright. In conclusion, it can be stated that the presence of nanotechnology opens up new vistas for developing novel nanoparticle-based drug formulations to achieve safer pulmonary drug delivery in the treatment of chronic diseases, however thorough physicochemical and nanotoxicological analysis for possible human application is needed.

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