Chapter 1

EMERGING NANOTECHNOLOGY IN CHRONIC RESPIRATORY DISEASES

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Abstract

A large population, including people of all age groups are suffering from chronic respiratory diseases worldwide. Asthma, chronic obstructive pulmonary disease, occupational lung diseases, cystic fibrosis, etc. are the most common of these diseases, and are non-curable with conventional and currently available therapies. The nanotechnology is emerging as a great therapeutic promise in different spheres including the drug delivery systems and is becoming the technology of choice nowadays. The administration of drug *via* inhalation helps in avoiding the first-pass metabolism by targeted delivery to the affected site. It has been observed that there is a huge diversity in nanotechnology being used in pulmonary diseases and thus safety assessment is a challenging as well as important task. The present review focuses on some of the major emerging nanotechnologies for chronic pulmonary diseases and includes some latest studies in the field of nanomedicines.

Keywords: Chronic respiratory disease, Asthma, Nanotechnology, Liposomes, Dendrimers.

1.1 Chronic respiratory diseases

Chronic respiratory diseases (CRDs) affect millions of individuals globally and are considered as the most common inflammatory diseases. The World Health Organization (WHO) estimates that approximately 328 million people live with chronic obstructive pulmonary disease (COPD) and approximately 3 million individuals die each year due to COPD. COPD is currently the third leading cause of mortality worldwide (Cruz, 2007). In addition, the WHO also estimates the prevalence of asthma globally, which stands at around 235 million. Moreover, asthma is also the most common respiratory disease in children, and around 250,000 asthmatics die due to the diseases (Asher and Pearce, 2014). These two most common CRDs significantly affect the quality of life of these patients, notably reductions in physical activity, difficulties in breathing and increased mucus production and cough (Celli and MacNee, 2004). CRDs also exert enormous economic and social burden on both the patients and their families, as well as the healthcare system in terms of treatment cost and hospitalizations. Moreover, the cost attributed to disability-adjusted life years and loss of productivity also runs in billions (Guarascio et al. 2013).

COPD is characterized by progressive airflow limitation with poor reversibility, which is primarily related to inflammation of the lungs in response to noxious particles and gases (TO, 2018). The precise definition of COPD has been proposed by The Global Burden of Obstructive Lung Disease

(GOLD) as; "*COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases"* (Gold: https://goldcoped.org/). The major symptoms associated with COPD include chronic cough, increased mucus production/secretion and progressive dyspnea (breathlessness). COPD is often defined as a complex and heterogeneous lung condition that includes a number of pathological manifestations, mainly chronic bronchitis, and emphysema (enlarged airspaces and loss of lung elasticity). These pathological aspects vary to a greater extent between different COPD patients. Thus, the treatments need to be optimized based upon the clinical presentation of COPD patients, as well as the risk factors that are primarily implicated in the development of the disease. Cigarette smoke is the most important risk factor for COPD, which is a global trend, whereas air pollution and occupational exposure to chemical dust and fumes also contribute significantly to the development and progression of the disease in low- and middle-income countries (Barnes, 2003; Kc et al. 2018). Most importantly, COPD patients often exhibit frequent episodes of increased symptoms that may require changes in medication and hospitalizations. These episodic worsening of disease is termed as acute exacerbations of COPD (AECOPD), which are the most important predictors of mortality and morbidity in COPD patients. AECOPD could be caused by bacterial or viral infections or non-infectious causes (air pollution, allergens etc.) (Sapey and Stockley, 2006).

Asthma is considered as a chronic disease that primarily affects proximal airways. Asthma is characterized by periodic symptoms, variable airflow obstruction and chronic inflammation of airways and lung tissues, e.g., airway smooth muscles (Bateman et al. 2008). Of particular interest is airway inflammation that results in a variety of asthma-specific pathological conditions. Also, asthma patients have been categorized into different clinical subtypes which are based up on the predominance of type of inflammatory cells in the pulmonary samples, such as sputum and bronchial biopsies (Wenzel et al. 1999; Simpson et al. 2006). Utilizing inflammatory cells as categorizing asthmatics, the patients are classified into four inflammatory subtypes, *i.e.,* neutrophilic, eosinophilic, mixed granulocytic and paucigranulocytic (Simpson et al. 2006). Moreover, adaptive immune response in asthma is further categorized as type I or type II responses. Type 1 immune response constitutes delayed hyper-sensitivity and increased the production of interleukin (IL)-2 and interferon(IFN)- γ. On the other hand, type 2 responses are

mediated by B-cell leading to humoral immunity and increased the production of IL-4, IL-5, IL-9 and IL-13 (Mosmann and Coffman, 1989).

Current therapies focus on reducing the symptoms of these CRDs. Targeting the inflammatory and pathological mechanisms involved in asthma and COPD will potentially reduce the burden of these chronic diseases (Dua et al. 2019). However, another major challenge remains when considering the optimal delivery of therapeutic compounds in the complex structures of the lung. For example, lung defence mechanism involves resistance and removal of any inhaled foreign particle by various physico-chemical mechanisms, such as muco-ciliary clearances (Newman, 2017). In addition, the poor delivery of these therapeutic compounds is further increased by the poor adherence to medications and/or inappropriate inhaler device techniques followed by patients with CRDs (Hickey, 2014). Hence, more innovative and effective routes of drug delivery are urgently required to treat these CRDs. There are several benefits of using inhalation route of drug delivery. The major comparison of inhalational route of drug delivery with other major routes is represented in **Fig 1**.

1.2 Pathophysiology of COPD and asthma

The major aspect of pathophysiology of COPD includes the progressive, non-reversible airflow limitation, which is largely attributed to both small airway disease (SAD) and emphysema. Both SAD and emphysema in COPD patients may commence at different stages of the disease history, as well as may greatly vary in terms of severity and its contribution to overall airflow limitation. Recent reports also highlighted that ~50% of small airways are effectively obliterated even before any observable clinical symptoms may appear (Koo et al. 2018). This is simultaneously accompanied by more detectable symptoms of increased mucus production in the large airways, which later manifests as chronic cough. Emphysema is a condition characterized by irreversible enlargement of lung air sacs, along with the destruction of alveolar sans fibrosis. Also, destruction of parenchymal tissues is also observed (Pahal and Sharma, 2019). Collectively, these pathophysiological processes result in significantly decreased lung function and increased risk of frequent bacterial/viral infections, which is termed as acute exacerbations (AE) (Agustí and Celli, 2017). Small airway narrowing is also attributed to an increase in lymphoid follicle formation, as well as collagen deposition around the airways.

Asthma is another important chronic inflammatory disease that is characterized by the hyper-responsiveness of the airways resulting in repeated wheezing, breathlessness, tightness of chest and cough. Chronic inflammation is a major feature of asthma, which involves infiltration of immune cells (neutrophils, eosinophils, lymphocytes, mast cells etc.) that then lead to the hallmark structural changes in asthma include hypertrophy of smooth muscle layer, sub-basement fibrosis, destruction of elastic fiber, hyperplasia of goblet cells and glandular submucosa, edema and desquamation of epithelium in airways (National asthma: https://www.ncbi.nlm.nih.gov/books/NBK7223/). Again, asthma is a heterogeneous disease and the concept of personalized medicine should be the way forward for both prevention and treatment (Pavord et al. 2018).

1.3 Introduction to the drug delivery in respiratory diseases

In recent times, inhalation therapy has been an important route for targeting respiratory diseases via reduction in localized symptoms including airways inflammation and constriction. Several inhalation devices have been used such as nebulizers, dry powder inhalers (DPI), pressurized metered dose inhalers (pMDI), soft mist inhalers that can lower the dose with therapeutic equivalence and reduce the systematic side effects associated with the oral or intravenous delivery (Winkler et al. 2004). Drug deposition via inhalation is determined by particle size, aerosol velocity and inspiratory flow. Inhaled drugs include corticosteroids, beta-sympathomimetics, muscarinic antagonists, and antibiotics (Dozor, 2010). Commonly inhaled corticosteroids, bronchodilators, mast cell inhibitors, leukotriene receptor antagonist, muscarinic antagonists, anticholinergics and methyl xanthenes are prescribed therapies especially in asthma and chronic obstructive pulmonary disease (COPD). Inhaled corticosteroids have an anti-inflammatory effect and are effective against asthma but their role is conflicted in COPD. Bronchodilators include β agonist (short acting β agonist-SABA and long acting β agonist), theophylline and anticholinergics. Glucocorticosteroids had been the major therapy for asthma while PDE4 inhibitors, NFκB inhibitors, MAPK p38 inhibitors, ß2-agonists and corticosteroids have been important therapeutics for COPD (Barnes, 2011). However, they did not reduce the disease progression and inflammation which manifests the need for potential therapeutics to reduce the pathology of the disease.

Inhalation therapy is advantageous as there is increased bioavailability of the drug since lungs have restricted intracellular and extracellular drug metabolizing enzymes (Loira-Pastoriza et al. 2014). It also reduces non-reversible tissue damage caused by cytotoxicity of drugs. There is a reduction in dose, high absorption leading to rapid action (Loira-Pastoriza et al. 2014; Ruge et al. 2013). Furthermore, the bio-barriers such as mucus, macrophages and ciliated cells limit the drug localization, penetration and absorption. For effective drug delivery to lungs, drug such be localized to target site, should be able to penetrate through mucus and escape the bio-barriers (Dua et al. 2019; Hamman et al. 2005). It is an important need to identify new therapies against different respiratory diseases including COPD, asthma, lung cancer and pulmonary infections (Hamman et al. 2005). Some of the important instances highlighting the novel drug delivery systems are:

Chennakesavulu *et al.* worked on the delivery of liposome encapsulating budesonide and colchicine against Idiopathic Pulmonary Fibrosis. *In vivo* studies on adult male Wistar rats *via* inhalation which shows reduced systemic absorption and these liposomal dry powders were stable for 6 months (Chennakesavulu et al. 2018). Further, it has been studied that saturated egg phosphatidylcholine (EPC) and cholesterol liposome encapsulated with Ketotifen fumarate, an antiasthmatic drug. The successful synthesis and delivery through DPI of the liposome has been reported in COPD/asthma (Joshi and Misra, 2001). Polymeric micelles of polyethylene glycol (PEG) and 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) encapsulating budesonide fabricated via coprecipitation method delivered to COPD rat model has better dissolution compared to budesonide. Furthermore, it has shown a decrease in inflammatory cells in bronchoalveolar lavage fluid (BALF) (Sahib et al. 2011). Researchers have assessed BSA nanoparticles encapsulated with DOX for the regeneration of the extracellular matrix (ECM) for emphysema. *In vivo* studies show a significant decrease in MMPs in lungs for upto 4 weeks in rat model. Therefore, elastic tissue regeneration could be significant for unmet need for COPD treatment (Parasaram et al. 2016).

1.4 Nanoparticles and similar vesicles such as solid lipid nanocarriers in respiratory diseases

Inhaled drug delivery systems nurtured in the treatment of various chronic lung disorders. There is a need for confined and prolonged drug release in the lungs, which is more anticipated in targeting. The lipid-based formulations in nanocarriers solid lipid nanocarriers (SLNs) and

nanostructured lipid nanocarriers (NLCs) became an attractive strategy for delivery of poorly soluble drugs.

SLNs are aqueous dispersions prepared using solid lipids consisting of triglycerides and phospholipids. As the composition for the preparation of SLNs includes physiological compatible lipids, these preparations are less toxic and highly adequate for delivery of therapeutics by the respiratory route. The components used in SLN help in conserving the optimal surface tension at the alveolar surface and reduction of friction at lung tissue. Due to the low toxicity and utilization of physiologically compatible lipids, SLN based formulations have endured as prevailing drug delivery system (Paranjpe and Müller-Goymann, 2014; Beloqui et al. 2016; Dua et al. 2019).

SLNs based formulations hold numerous benefits such as avoidance of organic solvents in the process of preparation, high drug loading, improve the drug stability with minimum interaction with the external environment, provide controlled release of the drug and drug targeting. SLNs based formulations exhibit certain drawbacks such as aggregation on storage, gelation propensity, polymorphic transitions of lipids and low amalgamation of the drug due to the formation of the perfect crystalline lattice of lipid. There are some efforts were made to overcome these issues with the newer generation of lipidic nanocarriers including nanostructured lipid nanocarriers, lyotropic liquid crystalline nanoparticles, and lipidic nanospheres (Girdhar et al. 2018; Singhvi et al. 2018).

Nanostructured lipid carriers are amongst the second-generation lipid nanocarriers developed with a combination of liquid lipids and solid lipid. The liquid lipid is enclosed into a solid lipid matrix which prevents coalescence and strongly immobilizes the drug. In NLCs, the liquid oil is blended with solid lipid to impart the imperfections in crystal order of solids. The additional liquid lipid increases the entrapment efficiency and decreases the drug leaching on storage (Khosa et al. 2018).

SLNs and NLCs have been explored for respiratory diseases. These lipidic nanocarriers provide drug targeting and prolonged release (Dua et al. 2018). Islan *et al* reported encapsulation of levofloxacin-based SLNs and NLCs based formulations for the treatment of recurrent infection caused by *Pseudomonas aeruginosa*, particularly in cystic fibrosis. SLNs were prepared using myristyl myristate (Crodamol™ MM), Pluronic F68 using ultrasonication method. Crodamol™ GTCC-LQ oil was added 3% weight of lipid in case of NLCs formulation. SLNs based formulation showed entrapment efficiency of 20.1 ± 1.4%, whereas 55.9 ± 1.6% was observed in NLCs based

formulation. The report reveals controlled drug release in case of NLCs based formulation in comparison to SLNs based formulation. DNase enzyme was amalgamated into NLCs based formulation, to improve the antibiotic diffusion by decreasing the viscoelasticity of mucus which was observed in the lungs of cystic fibrosis condition. The results demonstrated that formulation showed resilient antibacterial activity against gram-negative bacteria *Pseudomonas aeruginosa* and gram-positive bacteria Staphylococcus aureus. *In vitro* antimicrobial assay of levofloxacin loaded NLCs showed complete destroyed the biofilm of Pseudomonas aeruginosa which is the most pertinent pathogen in cystic fibrosis (Islan et al. 2016).

Rosiere and his colleagues developed paclitaxel loaded SLNs. The SLNs surface was modified by coating with folate grafted copolymer of polyethylene glycol and chitosan (F-PEG-HTCC). The prepared formulation showed 99.0 ± 0.3% encapsulation efficiency with 4.6 ± 0.1% drug loading and particle size was found to be 249 ± 36 nm (0.31 particle size distribution). The *in vitro* studies performed in M109-HiFR cells and results exhibited the decreased inhibitory concentrations (60 nanomolar) with paclitaxel-loaded in F-PEG-HTCC-coated SLNs compared to free taxol (340 nanomolar). The *in vivo* studies revealed an increase in localization of paclitaxel in tumor tissue and minimal systemic absorption by pulmonary delivery in case of F-PEG-HTCC-coated SLNs. The F-PEG-HTCC-coated SLNs was distributed throughout lung tumor after pulmonary delivery regardless of blood vessels. The F-PEG-HTCC-coated SLNs exhibited high antiproliferative activity compared to PEG-HTCC-coated SLNs. It was expected due to increased uptake of F-PEG-HTCC-coated SLN by multiple pathways. It is concluded from the study that the folate receptor was found to exhibit an important role in drug targeting with the anti-proliferative activity (Rosière et al. 2018).

In an investigation, phosphodiesterase type-5 inhibitor sildenafil citrate was loaded in SLNs based formulation for the treatment of pulmonary hypertension. SLNs based formulation was developed for pulmonary delivery of sildenafil citrate to overcome high first-pass metabolism, low oral bioavailability (40%) and short half-life (3-5 h). The developed lipid-based formulation was investigated for their potential to retain their properties after nebulization and autoclaving. The prepared formulation exhibited encapsulation efficiency in the range of 88-100% with sustained release of the payload over 24 hours. The results showed no alteration in SLNs properties after nebulization with a jet nebulizer and autoclaving for 20 minutes at 120°C. The SLNs based

dispersion was evaluated for interaction with mucin, which was determined by turbidimetrically. Results showed the increased size and zeta potential which indicated the adherence of mucin on the surface of SLNs (Makled et al. 2017).

In a study, methyl α-d-mannopyranoside surface modified SLNs formulation of rifampicin showed improved targeting towards macrophages. Mannose was used for surface modification to increase internalization due to mannose receptors located on infected alveolar macrophages. Cytotoxicity and cell internalization were studied on J774 murine macrophage cell line. MTT (3-(4,5 di-methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay results demonstrated dose-dependent cytotoxicity and cell viability was reduced by <80% after 24 hours. Cell internalization study results exhibited quick uptake of mannosylated SLNs by macrophages. The cell internalization was observed under confocal microscopy with blue stained nuclei in J774 cell monolayer. The results detailed active targeting was achieved in case of SLNs coated with Methyl α-d-mannopyranoside (Maretti et al. 2017).

Vieira and co-authors reported the improvement of tuberculosis management by mucoadhesive chitosan coated SLNs loaded with rifampicin. Designed chitosan coated SLNs were evaluated for mucoadhesive property and permeability in alveolar epithelial cells A549. Results showed significant permeation in the case of chitosan-coated SLNs compared to non-mucoadhesive SLNs (Vieira et al. 2018).

Sastre *et al*. developed tobramycin loaded NLCs for *Pseudomonas aeruginosa* infections associated with cystic fibrosis. Hot melt homogenization technique was utilized for the preparation of NLC. *In vitro* release studies showed a biphasic drug release profile characterized by an initial burst release followed by a sustained and progressive release of tobramycin. It is expected that initial high release can contribute to inhibiting the biofilm growth and later sustained release can provide prolong lung exposures. Such a biphasic release pattern can reduce the number of dose and dosing intervals. The cell viability studies indicated that there was no decrease in viability after treatment with tobramycin NLCs dispersion. There was no effect of mucolytic agents on NLCs dispersion which was studied on artificial mucus barrier. *In vivo* pulmonary administration of infrared dye-labeled lipid nanoparticles by Penn century® device showed an extensive distribution in the lungs for 48 h (Moreno-Sastre et al. 2016).

SLNs based formulation was utilized for delivery of protein plasmid (pEGFP) and doxorubicin for lung cancer. Target based approach was utilized for delivery of gene and drug, by modifying the surface of SLNs using transferrin ligands. The particle size of optimized nanoformulation was 267 nm with a zeta potential of +42 mV. *In vitro* transfection efficiency of the developed formulation was estimated on Adenocarcinoma cell line (A549 cells). Transferrin coated SLNs with doxorubicin and protein plasmid exhibited higher transfection efficiency compared to SLNs without transferrin coating and naked plasmid protein. *In vivo* anti-tumor efficiency was observed in mice bearing A549 tumor. The transferrin coated SLNs with a combination of doxorubicin and plasmid (gene) demonstrated higher anti-tumor efficacy with smaller tumor volume compared to non-coated SLNs (Han et al. 2014).

NLCs based formulation was reported for simultaneous delivery of anticancer and siRNA specifically to lung cancer. The objective of co-delivery was to overcome multidrug resistance by siRNA and drug was used to induce cell death. Two siRNA were evaluated to overcome multidrug resistance, which includes siRNA targeting MRP1 mRNA responsible drug efflux transporter. Another siRNA targeting BCL2 mRNA which suppresses cellular anti-apoptotic defense. The prepared NLCs preparation was compared with intravenous injection and inhalation. The inhalation therapy showed improved lung accumulation whereas intravenous injection led to accumulation in liver, lung, kidney, and spleen fewer quantity reached into lung tissue. The inhalation therapy of NLCs was effectively delivered the drug and siRNA in cancer cells. Gene silencing and cell death were observed in lung tumor cells (Taratula et al. 2013).

Payne and his co-workers encapsulated all-trans retinoic acid in SLNs using emulsification-ultrasonication method. The developed formulation was evaluated on immunomodulatory A549 cells, which declined pro-inflammatory IL-6, and IL-8 levels indicating a promising approach for local immunomodulation in chronic obstructive pulmonary disease. The A459 cells were evaluated for human mesenchymal stem cells containing hydrogel formulation which resulted in the increase in IL-6 and IL-8 levels indicating pro-inflammatory effect. The combination of SLN based all-trans retinoic acid and human mesenchymal stem cells exhibited potential anti-inflammatory activity (Payne et al. 2019).

1.5 Liposomes in respiratory diseases

Liposomes are colloid based drug delivery system composed of lipid layer with the aqueous center. Therefore, they are suitable for encapsulating lipophilic and hydrophilic drugs and are suitable for pulmonary drug delivery via inhalation for localized drug delivery allowing prolonged action of drug with decreased toxicity (Chellappan et al. 2018; Ng et al. 2018). Such a delivery system improves the pharmacokinetics of drugs especially the poor water soluble anti-cancer drugs such as Paclitaxel (Kiparissides and Kammona, 2008). However, liposomes are less stable and have a small shelf life so surface modification with ligands is being carried out. This leads to increased stability, shelf life, adhesion and permeability. Different polymers used to improve adhesion and target specificity are polyethylene glycol (PEG), chitosan, carbopol, hyaluronic acid, etc (Dua et al. 2019; Mehta et al. 2019). Liposomes can be cationic for gene delivery and anionic for targeting alveolar macrophages. Several studies prove that liposomes can be used for gene therapy, anti-microbial, anti-diabetic agent etc. FDA has also approved liposomal drug delivery of Amikacin by Insmed for nebulization (Zylberberg et al. 2016).

Frankenberger *et al* investigated the role of liposomal methyl predniosolone (MP) in lipopolysacchride mediated proinflammatory tumor necrosis factor (TNF) and anti-inflammatory interleukin-10 (IL-10) in aleveolar macrophages (AM). This liposomal mediated drug increased the IL-10 production and reduced TNF after exposure to macrophages. It was concluded that liposomes can be used for localized delivery of glucocorticoids with less side effects (Frankenberger et al. 2005). Chono *et al* demonstrated the uptake of mannosylated liposomes in comparison to non-mannosylated liposomes in rat alveolar macrophages post intratracheal administration (Chono et al. 2007). Further, Joshi and Misra observed the delivery of ketofin fumerate as a liposomal dry powder in rat lungs for stabilizing mast cells against asthma inflammatory response (Joshi and Misra, 2003). Alvarez *et al* reported liposomal entrapment of *Dermatophagoide spteronyssius* vaccine against asthma. It has been reported to prevent worsening of asthma by reducing the inflammatory response (Alvarez et al. 2002). Liposomal formulation of Cisplatin is in clinical trial phase I for successful drug targeting with prolonged exposure and minimal side effects (Wittgen et al. 2007). Pulmaquin™ is dual liposomal ciprofloxacin used *Pseudomonas aeruginosa* infections with noncystic fibrosis bronchiectasis. It has sustained drug release with the minimal side effect (Serisier et al. 2013).

Khademi *et al* reported the use of cationic liposomes as adjuvants, with enhanced potency for various tuberculosis subunit vaccines with increased therapeutic effect by inducing memory to the immune system (Schmidt et al. 2016). Further, it has been reported that cationic liposomes combined with De-O-Acylated lipooligosaccharide can improve the effectiveness as for targeting Th1-type immune cells in tuberculosis. Nkanga et al studied crude soybean lecithin liposomes comprising isoniazid. These liposomes are effective in pulmonary delivery in treating tuberculosis (Nkanga et al. 2017).

1.6 Dendrimers and micelles in respiratory diseases

In the advancement of formulation techniques, a new class of substance have become significantly useful, in overcoming several drug delivery issues in formulation development. These are called dendrimers. Being unique in their primary architecture, these compounds have typical molecular properties that help in the design and development of nanodrugs and nanoformulations. Lately, these substances have gained much attention especially, in terms of research and development of newer and effective carrier systems (Dufès et al. 2005).

Dendrimers primarily have defined structures which are versatile in delivering drugs. These materials are rapidly emerging due to their high acceptability and robustness. They also have good functionality. There are two major mechanisms by which dendrimers exert their activity; firstly, by entrapping high molecular weight substances, and secondly, by conjugating. Most of the substances those conjugated are hydrophilic and hydrophobic materials. The potentiality of dendrimers in entrapment is accomplished by a host to guest participation. Delivery of a range of several entities are made possible with the employment of dendrimers, especially because of its unique structure (Madaan et al. 2014). Lately, more and more newer drug carriers are being designed with the help of dendrimers, which are turning to be promising therapeutic substances in several biomedical applications.

Dendrimers have unique and specific properties. Being profusely branched and organised uniquely, these three-dimensional molecules have considerably lower polydispersity ratio. *'Dendron'* means *'tree'*, which resembles the extremely branched structure of the dendrimers. Each new branch is termed as 'generation'. These are sometimes referred to as *'layers'* (Tomalia et al. 1985). Dendrimers are being extensively used in nanomedicine. The entire structure

conforms to a cascading pattern, with an inner core moiety. The adjacent layers contain functional groups.

Therapeutic substances that have formulation drawbacks primarily in terms of their pharmacokinetic profile or their pharmacodynamic profile, can improve such parameters with the help of dendrimers. In addition, formulations that incorporate low molecular weight substances in them can also be effectively formulated with dendrimers. Low molecular weight moieties are also known to have developed with the incorporation of such dendrimer polymers. Various biological fluids can also be analysed and used in the diagnosis of markers, as dendrimers can be conjugated with several types of antibodies and image enhancement markers (Bai et al. 2006). Due to their applications, now these substances are being widely employed and used in the field of pharmaceutical sciences. In addition to the above, dendrimers can also be used as bioavailability enhancers and as agents that modify the release of the drug.

There are several types of dendrimers that are being tested and used in the delivery of nanosubstance and drugs. The most common ones are the polyamidoamine (PAMAM) types. These are followed by poly-propylene imine (PPI) and poly-ether hydroxylamine (PEHAM). Some other less common types are poly-esteramine (PEA), poly-L-lysine, melamine and polyglycerol types. Most of these dendritic types are tested for their drug delivery properties (Wolinsky and Grinstaff, 2008).

There are several advantages that are possessed by the dendrimers in terms of a typical drug carrier system. These substances have relatively higher water solubility (Duncan and Izzo, 2005; Soto-Castro et al. 2012). In addition, they also possess biocompatibility and polyvalency. Moreover, they also have accurate molecular weights (Tomalia, 2005; Patton et al. 2006).

There are several advantages and applications of dendrimers. Patri *et al*., reported the delivery of monoclonal antibodies by using prostate specific membrane antigen (PSMA) (Patri et al. 2004; Wu et al. 2006). The results were significant in the delivery of the antibodies to the prostate tumours. In a similar mechanism, several researchers have succeeded in delivering methotrexate to brain tumour tissues (Shukla et al. 2008). This shows that dendrimers can be used for drug delivery to tumours.

1.7 Dendrimers for pulmonary delivery

Dendrimers are also effective in delivering drugs to the lungs and the respiratory system. Shuhua Bai and colleagues have reported the use of dendrimers in the pulmonary delivery of enoxaparin, which eventually had resulted in the prevention of thrombotic events in blood vessels (Bai et al. 2007).

Calu-3, primary alveolar cell lines were studied for their successful intracellular uptake mechanisms using the PAMAM type of dendrimers. In addition, *ex vivo* studies were also performed using perfused rat lungs. Both the methods were successfully tested with the absence of aggregation with the fluid in the lungs (Morris et al. 2017). The results were promising in terms of target delivery to the lungs.

An *in vitro* model of the pulmonary epithelium was tested to study the effect of PEGylation when these were conjugated with PAMAM type of dendrimers. The findings showed that there was an increase in the PEG surface density when apical transport increased. This was also observed in *in-vivo* models (Bharatwaj et al. 2015).

Enhancement in the bioavailability of several peptides and hormonal proteins like insulin, calcitonin and other protein drugs were evaluated in rats. PAMAM type of dendrimers were employed in the study. Various layers or generations were used in addition during the study. The effects in the presence and in the absence of dendrimers were the focus of the study (Dong et al. 2011). The findings show that the dendrimers significantly enhanced the absorption in the lungs for the test substances. It was also observed that the effects were also dependent on the generations of the dendrimers.

1.8 Dendrimers in respiratory disorders

One of the most commonly used drugs during the occurrence of asthma is methylprednisolone. It is an important drug that belongs to the class of corticosteroid. The drug primarily reduces the inflammation that is associated with asthma. A study was done to evaluate the enhancement in the airway delivery using methylprednisolone-PAMAM dendrimer conjugate. The study was performed in an animal model of lung inflammation (Inapagolla et al. 2010). The results were determined based on the accumulation of eosinophils in the lungs. Ovalbumin was the allergen

used in the experiment. The findings showed that the dendrimers produced a significantly higher positive effect in treating the exacerbations of lung inflammation.

In another study, PAMAM type dendrimers were used to study the lung delivery of the drug beclomethasone. These dendrimers were tested as nanocarriers targeted towards lung delivery of this drug. In addition, several generations were also employed in the study. Beclomethasone is reported to have poor solubility (Nasr et al. 2014). The observations from the study revealed that, dendrimers significantly increased the delivery of the drug to the lung mucosa.

Chronic inflammatory conditions like asthma and COPD is reported to be treated with the help of targeted drug or RNA delivery to the lung endothelium. Small interfering RNA (siRNA) were used in the study which were conjugated with dendrimers that were modified chemically. A specific substitution process was adopted where the free amines on the dendrimers were exchanged for alkyl chains (Khan et al. 2015). The most promising material were used in the study to target the pulmonary endothelium. The findings were significant. In another study, it is reported that phosphorus-based dendrimers having, one of the compounds namely, pyrrolidinium or morpholinium were chosen for enhanced biocompatibility. Dendrimer complexes containing the former substance was reported to be having more significant complexation. The findings suggest that phosphorus-based dendrimers could play a major role in the pulmonary delivery of drugs and moieties (Adam et al. 2017).

Several studies have been reported for the delivery of drug material for cystic fibrosis. PAMAM based dendrimers have been widely used for cystic fibrosis condition (Brockman et al. 2017). In another study, it was reported that PAMAM dendrimers decrease infection and enhanced improvement.

Several functionally different and potent drugs targeting cancer cells combined together in a delivery module has shown to be a potent way of targeting lung cancers. Nevertheless, a powerful and effective drug carrier is the primary requisite for this. Dendrimers can be used efficiently in this regard to conjugate anticancer drug moieties that can be delivered to the site of cancer cells. This combinatorial drug delivery is shown to be positive in several cancer therapies (Amreddy et al. 2018).

In another study, camptothecin was studied with conjugated dendrimers as delivery carriers. It is reported by Morgan and colleagues that camtothecin was successfully delivered to the cancer cells (Morgan et al. 2003). In addition, it is reported that melamine-based dendrimers were employed to solubilize methotrexate. This is addition also reduced the toxicity of the drug (Neerman et al. 2004).

1.9 Microparticles/microspheres and microemulsion in respiratory diseases

Chronic respiratory diseases, such as asthma, COPD, cystic fibrosis, silicosis and pulmonary artery hypertension are the main source of morbidity and mortality around the world (Chellappan et al. 2017; Islam et al. 2017). This is principally a direct result of the maturing populace and expanding pervasiveness of cigarette smoking comprehensively. In this way, it is essential for an effective drug delivery system to convey the remedial moiety to the objective site at the correct time and in an appropriate amount especially with different chronic respiratory diseases, for example, asthma where a prompt therapeutic action is required (Kaur, 2017; Jasinski et al. 2017; Madni et al. 2017). Most of the conventional dosage forms have different constraints, for example, portion dumping, non-focused on impacts, multiple administration of medication prompting lesser patient consistence, which lead to the development and trends of novel drug delivery systems where nanotechnology is one of the key role players. Nanotechnology is an area in which the medication is combined into a nanosystems that give another dimension to the pharmacotherapy and have cell-focused on medication conveyance approach, which is required in majority of the chronic respiratory conditions (Taguchi et al. 2017; Yu et al. 2017).

Biological properties of nano-transporters like polymeric, liposomes and micelles can be changed and controlled by the necessity in this manner making them profoundly proficient for pharmacological and therapeutic purposes (Mehta, 2016; Momtazi-Borojeni et al. 2017). Improvement of nano-carriers has numerous points of interest, including productive conveyance and accumulation of medication in the affected area even with the physiological condition of compromised vascularization. Moreover, exploratory discoveries have demonstrated that nano-transporters display increasingly efficient tissue penetration thus bringing about expanded tissue explicit activity of medication contrasted with the regular drug administration routes (Abdelaziz et al. 2018; Cryer and Thorley, 2019). Despite the fact that utilization of the nano-transporter system is heavily debated inside the respiratory research network, yet this system offers

progressively proficient medication conveyance systems in pulmonary disorders. Accordingly, for characterizing novel drug delivery mechanisms in the time of modern medical science, nanoparticles offer an appealing idea for use in respiratory system (Abdelaziz et al. 2018; Cryer and Thorley, 2019; Li et al. 2019; Mehta et al. 2018; Thakur et al. 2019). This is fundamentally because of the moderately uniform appropriation of the medication tagged with nano- carriers inside the alveolar surface alongside improved dissolvability and delayed the release. These properties additionally decrease the recurrence of medication administration and improved patient consistence with least side effects (Hatamipour et al. 2018; Hema et al. 2018; Ihrie and Bonner, 2018).

1.10 Miscellaneous – Mucoadhesive drug delivery

1.10.1 Mucoadhesive nanoparticles

The purpose of developing mucoadhesive drug delivery systems is to prolong and intensify the contact between delivery carrier and the mucous apical pole, inducing active transport of macromolecular biopharmaceuticals across the biological barriers (Lehr, 2000; Smola *et al.*, 2008). Accumulation and retention of particles in the lungs due to the adhesion can lead to enhanced and sustained therapeutic effects and therefore decrease dosing frequency. This may lead to better patient compliance in chronic lung disease conditions since many of the commercially available inhalation therapeutics need to apply at least twice a day (Weber et al. 2014). The adhesion of nanoparticles to the mucus membrane can be due to the non-specific force (van der Waals forces, hydrogen bonding, electrostatic or hydrophobic interactions). Cationic surface charge nanoparticles play an important role in increasing its retention in the mucus membrane (Savla and Minko, 2013). A major limitation of mucoadhesive drug delivery systems is their non-specificity adhesion with respect to the substrate, undefined mucoadhesive time, and local side effects. In spite of these limitations, the modulation of epithelial permeability and inhibition of proteolytic enzymes can be done by mucoadhesive polymers.

Lectins are nonimmunological glycoproteins that have the capacity to recognize receptor-like structures of the cell membrane and bind to glycoproteins exposed at the epithelial cell surface (Lehr, 2000; Smola et al. 2008). Respirable aerosol of a lectin-functionalized liposomal carrier has been reported by Abu-Dahab *et al*. Cholesterol enhanced the stability of the liposomes during nebulization and upon incubation with pulmonary surfactant preparation. The synthesized

liposomes were able to bind to human alveolar cells (A549 and primary cells) (Abu-Dahab et al. 2001).

Amore *et al* synthesized fluticasone propionate loaded solid lipid microparticles using chitosan and alginate and evaluated to access the biocompatibility and effectiveness in controlling senescence and inflammatory processes in cigarette smoke extracts. The synthesized microparticles were found to be more effective than fluticasone propionate alone in controlling oxidative stress in lung inflammation, including ERK1/2 pathway activation and cigarette smoke extract-induced survivin expression (Amore et al. 2017). Chitosan IFN - γ-pDNA nanoparticles reduced the airway hyper-responsiveness and allergen-induced airway inflammation in BALB/c mouse model of allergic airway disease (Kumar et al. 2003). In a study, *M. tuberculosis* infected guinea pigs were treated with sodium alginate-chitosan based nanoparticles containing antitubercular drugs for a period of 15 days. At the end of the study, no *M. tuberculosis* bacteriums were observed the infected lungs treated with mucoadhesive nanoparticles (Zahoor et al. 2005).

Lee *et al* found the improved theophylline delivery from thiolated chitosan nanoparticles in ovalbumin sensitized BALB/c mice model of allergic asthma. The intranasal delivery of nanoparticles increased the anti-inflammatory effects of theophylline compared to pure theophylline (Lee et al. 2006). Chitosan-coated polylactic-co-glycolic acid nanoparticles synthesized by a multiple emulsion solvent evaporation technique may open up a new avenue for efficacious treatment of lung-fungal infection. Tc-99m-labeled nanoparticles had better pulmonary retention for a longer period. A significant improvement in the pharmacokinetic profile of voriconazole was found from chitosan-coated nanoparticles (Paul et al. 2018). Heparin containing nanoparticles of chitosan and hyaluronic acid have shown promising results in the management of asthma in rat models (Oyarzun-Ampuero et al. 2009).

Successful co-delivery of pemetrexed (a synthetic chemotherapeutic agent) and resveratrol (herbal cancer chemo preventive) has been reported from lyotropic liquid crystalline nanoparticles prepared by a hydrotrope method for effective management of lung cancer. Cetyl trimethyl ammonium bromide was used to increase the encapsulation of pemetrexed by hydrophobic ion pairing. The results demonstrated concentration and time dependent cytotoxicity profile against A549 lung cancer cells. Nanoparticles administered mice models, with urethane induced lung

cancer, demonstrated promising results in tumor growth inhibition via inhibition of angiogenesis and induction of apoptosis (Abdelaziz et al. 2019).

Wheat germ agglutinin coated lectin-functionalized poly(lactide-co-glycolide) (PLGA) based bioadhesive nanoparticles (350-400 nm) have been reported by a two-step carbodiimide procedure to deliver anti-tubercular drugs. The *in vivo* performance of synthesized nanoparticles was studied in guinea pigs through the oral/ aerosol route. Following administration of coated nanoparticles to the animal models, the plasma drug concentration was maintained for 6-7 days for rifampicin and 13-14 days for isoniazid and pyrazinamide. The results of mycobacterial colony forming units revealed that three doses of lectin-coated nanoparticles, after every 14 days interval, were as much effective as 45 dosages of pure drug solution (Sharma et al. 2004). Tureli *et al* found that the ciprofloxacin loaded PLGA nanoparticles synthesized by microjet reactor nanoprecipitation method are safe and effective against *Pseudomonas aeruginosa* infections in cystic fibrosis lung. The outcomes of cytotoxicity study in Calu-3 HTB-55 bronchial epithelial cell line (model for healthy lung) and CFBE41o$^-$ cystic fibrosis-derived bronchial epithelial cell line (model for diseased lung) suggested that the nanoparticles are well tolerated by the epithelial cells and showed low cytotoxic potential (Tureli et al. 2017). Surface conjugated PLGA nanoparticles of chitosan have shown efficient targeted delivery and improved oral bioavailability of itraconazole to clear lung infections in *Cryptococcus neoformans* infected mouse models (Tang et al. 2018). Chitosan (molecular weight 90-150 kDa) coated PLGA nanoparticles sustained release of tobramycin over a period of two days. The mucoadhesive nanoparticles, prepared by a solvent-evaporation method, had chitosan concentration dependant activity against *P. aeruginosa* (PA01 strain) (Al-Nemrawi et al. 2018). Inhaled chitosan-coated, PLGA nanoparticles exhibited a sustained release profile of tacrolimus with a lesser dose and side effects in the treatment bleomycin-induced pulmonary fibrosis (Lee et al. 2016). The study conducted by Zou *et al* explored the potential of PLGA nanoparticles as a non-viral vector for lung cancer gene therapy. The PLGA nanoparticles were prepared using Carbopol 940 and Pluronic. Carbopol stabilized PLGA nanoparticles demonstrated higher transfection efficiency in A549 cells comparing to Pluronics stabilized nanoparticles or naked DNA (Zou et al. 2009).

Conclusion

Nanocarrier systems have been found to provide the advantage of sustained-drug release in the lung tissue resulting in improved patient compliance by reducing dosing frequency. In the present review, potential benefits of nanomedicines in pulmonary diseases have been summarized. Nanotechnology has been observed to be a potentially beneficial approach for the diagnosis and treatment of pulmonary diseases. Various studies have demonstrated promising advancements, efficacy and safety of NPs for use in pulmonary diseases. However, significant challenges are still there in making nanotherapeutic approaches fully functional in clinical practice. Further studies are required to be done focusing majorly on determining the mechanisms of action of NPs in the treatment of chronic pulmonary diseases and improving their chemical structure to develop the desired nanomedicine or nanotherapeutics.

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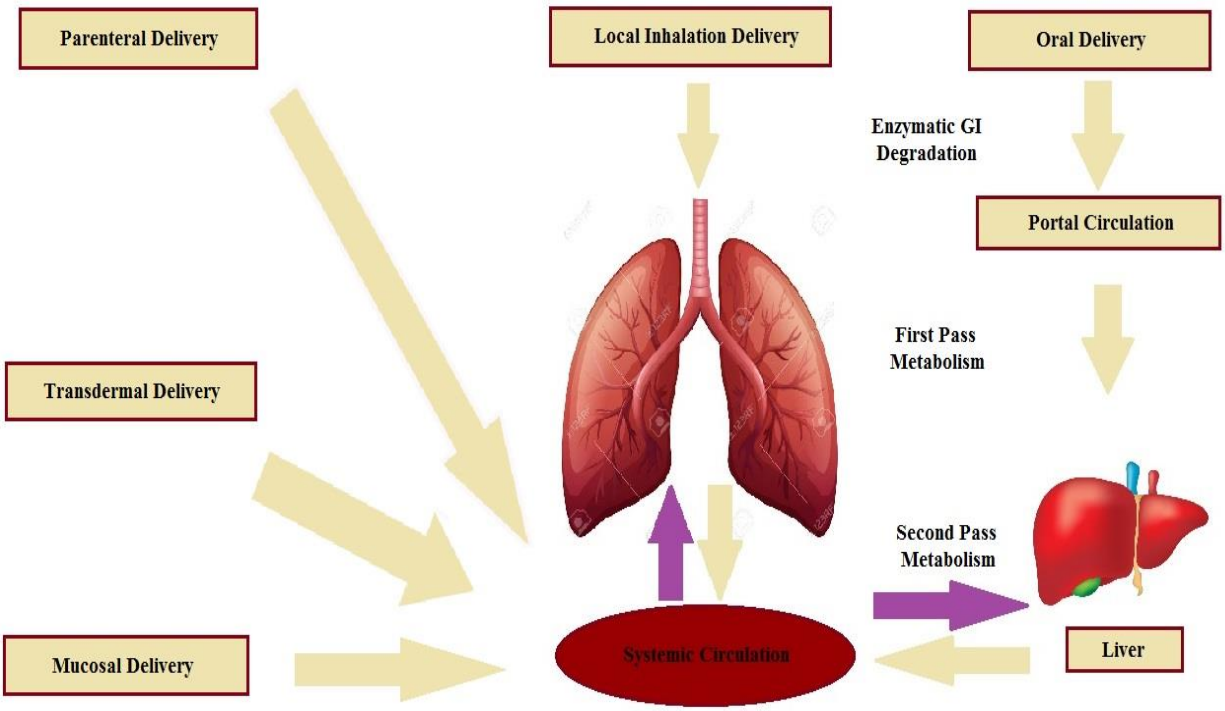

Fig 1. Inhalational route of drug delivery.