# Nanotechnology based advanced therapeutic strategies for targeting interleukins in chronic respiratory diseases

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# Abstract

Both communicable and non-communicable chronic respiratory conditions have accorded for suffering of millions of people of all ages and stated to be leading cause of death, morbidity, economic and social pressures, and disability-adjusted life-years (DALYs) worldwide. These illnesses impair patient’s health and negatively impacts families and society, particularly in low and middle-income countries. Chronic respiratory diseases (CRDs) affect different organs of respiratory system, involving airways, parenchyma, and pulmonary vasculature. As the number of respiratory diseases are exponentially escalating but still the stakeholders are not paying attention towards its serious complications. Currently, the treatment being used primarily focusses only on alleviating symptoms of these illness rather delivering the therapeutic agent at target site for optimal care and/or prevention. Lately, extensive research is being conducted on airways and systemic inflammation, oxidative stress, airway, or parenchymal rehabilitation. From which macrophages, neutrophils, and T cells, as well as structural cells as fibroblasts, epithelial, endothelial, and smooth muscle cells have been found to be active participants that are involved in these chronic respiratory diseases. The pathogenesis of all these chronic respiratory diseases gets caused differently via mediators and proteins, including cytokines, chemokines, growth factors and oxidants.

Presently, the target of prescription therapies is to reduce the inflammation of airways and relieve the airway contraction. In all studies, cytokines have been found to play an imperative role in fostering chronic airway inflammation and remodelling. Owing to the limitations of conventional treatments, the current review aims to summarize the current knowledge about the chronic respiratory disease and discuss further about the various conventional methods that can be used for treating this ailment. Additionally, it also highlights and discusses about the advanced drug delivery system that are being used for targeting the interleukins for the treatment of CRDs.

**Keywords:** Interleukins; chronic respiratory diseases; drug delivery

# Introduction

Globally, the health of the people is deteriorating and number of cases of people suffering for CRDs is exponentially increasing [1]. There is an increasing prevalence and burden of chronic respiratory diseases (CRDs), which has affected the lives of over 1 billion people globally and are a major cause of morbidity and mortality [2][3]. The high prevalence of CRDs has led to the severe level worldwide [4]. In 2017, 3·9 million deaths were accounted for CRDs (an upsurge of 18 percent since 1990) and accounted for 1470 DALYs per 100,000 persons (112·3 million total DALYs, a rise of 13·3 percent since 1990) [5]. CRDs have become serious public health issue in all nations around the globe, especially in developing countries and in underprivileged communities [6]. The prevalence of CRDs is rising everywhere, primarily affecting elderly people and children [7][8][9]. Acute Respiratory Distress Syndrome (ARDS), Asthma, chronic obstructive pulmonary disease (COPD), Pulmonary Fibrosis, etc., are the respiratory diseases that have affected more than 354 million global deaths from respiratory diseases [10]. COPD (3·9 percent of worldwide prevalence) and asthma (3·6 percent) are the most common CRDs [5]. It could be expected that SARS- CoV-2 and more serious COVID-19 infections would increase in patients with CRDs, especially in case of asthma and COPD [11–15].

In the coordination of inflammation and immune responses cytokines play a key role [16]. Cytokines are small secreted regulatory proteins that serve essential immunological functions. Cytokines contribute and control multiple roles, including cell proliferation, cell development, cell-cell communication and gene expression induction [17]. Each cytokine works by attaching to those receptors on target cells; the mode of action can be autocrine, paracrine and/or endocrine, according to the types of cells that produce one cytokine and/or express their receptor [18]. Cytokines play a major role in fostering chronic airway inflammation and remodelling, by influencing and encouraging cell-cell interactions [19]. Cytokine inhibitors are important in arranging and perpetuating chronic airway inflammation. Other than this, the involvement of interleukins (ILs) in various diseases and cellular processes makes it the potential for treating CRDs.

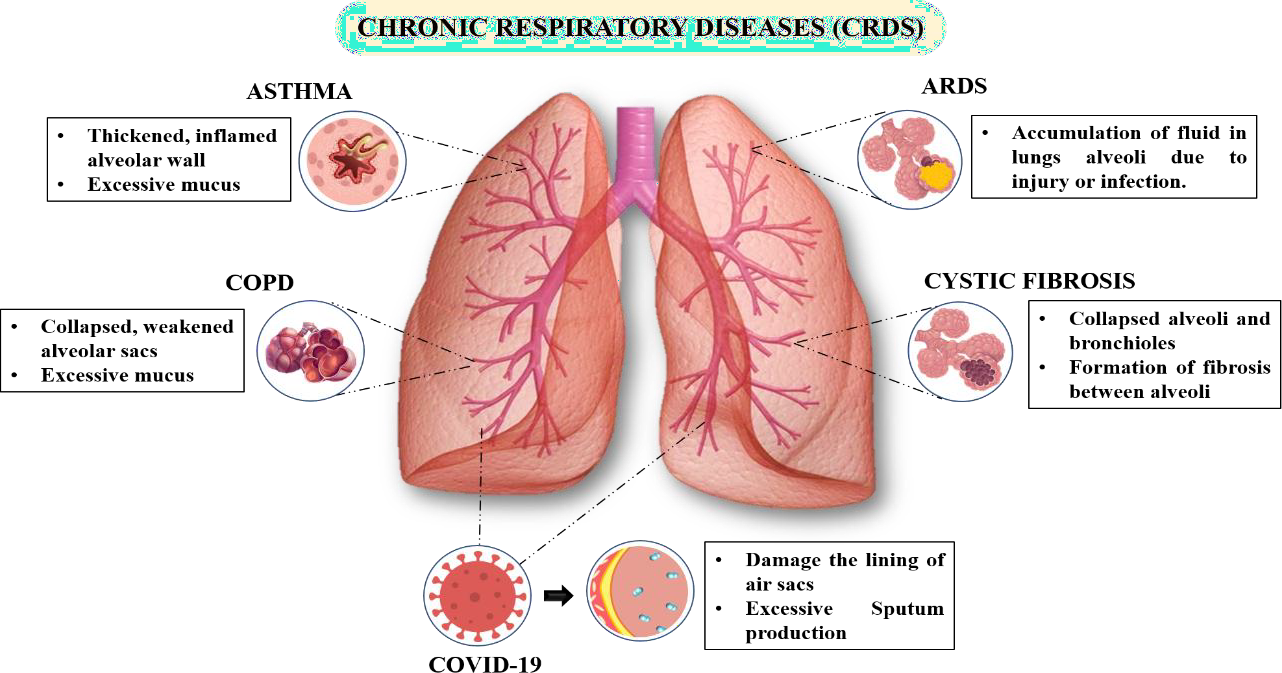
The traditional treatment approach for treating CRDs available in market includes antibiotics, anti-inflammatory medications, corticosteroids, and leukotriene pathway inhibitors (5- lipoxygenase inhibitors and antagonists of the leukotriene receptors), and bronchodilators.

These remedies are not fully effective in eliminating these CRDs, instead they are associated to induce certain side effects and sometimes leads to the addiction to steroids. These complications have prompted us to systematic search for new targets and therapies for treating these respiratory disorders. Owing to these limitations, the exploration of novel drugs has become the priority for pharmaceutical and academic scientists [20][21][22][23]. The issues like adherence and tolerance against traditional drugs is an another issue that has motivated for exploring and forming new drugs [24]. Lately, novel drug delivery systems have emerged as an effective approach, which is also found to be effective in overcoming the limitations of conventional drug delivery systems and prominent enough to meet the need of the healthcare profession. In recent years, research and applications in nanotechnology and nanoscience have undergone extraordinary progress [25]. There has been substantial increase in interest in progressive new drug delivery approaches employing cutting-edge nanotechnology. Nanoparticles are considered as a candidate for safely transporting therapeutic agents in a specific organ, tissue, or cell compartment [26]. As an innovative technique for drug delivery, recent development in nanoparticles has shown tremendous potential [27].

Thus, this review is aimed to comprehend to the existing knowledge about the CRDs and traditional medication that is being used for treating it. Furthermore, it also highlights the interleukins as therapeutic target for the treatment of respiratory disorders with emerging novel drug delivery approach.

# Global Prevalence of Chronic Respiratory Disease

The immense health burden of chronic respiratory diseases has enclosed the global population. The silent epidemic of CRDs have become a chief factor responsible for world mortality/morbidity rate. The common CRDs are illustrated below in the **Figure 1.**



**Figure-1:** Diagrammatic representation of various chronic respiratory diseases

# Asthma

Asthma is a chronic pulmonary disease with increased airway irritability, characterised by frequent episodes of severe blockage of the airways that resolve spontaneously or after proper treatment [28]. Asthma is common, and about 300 million people worldwide now have asthma and there are reports that the incidence of asthma worldwide is rising 50 percent per decade [29][30][31][32]. It represents clinical signs such as wheezing, night cough, breath shortness, tightness of the chest, and variable limits of expiratory airflow. Symptoms fluctuate over time and can get worse leading to respiratory failure [33]. Many harmful substances found in air may cause blockage of airways. In many nations of the globe, it is considered that industry is the biggest contributor that produces harmful compounds into the environment [34]. In the United States and many other western countries, morbidity and mortality from asthma tend to be on the rise. In the United States and Canada, mortality rates decreased between 1965 and 1978 and then rose again [35]. In the Western world, asthma prevalence and occurrence are very high. There's a general concern that the incidence of asthma in developed countries is still growing, but in developing countries already increasing incidences are being recorded, from these the economic and humanitarian consequences of asthma are likely to become greater [36]. In various countries, the prevalence of asthma in children showed substantial geographical variation from 2 to 32% [37]. For the treatment of

asthma, since 1952 corticosteroids have been used increasingly, and since 1960 the use of pressurized aerosols containing sympathomimetics in Great Britain has rapidly increased [38].

# Acute Respiratory Distress Syndrome (ARDS)

In 1967, Dr. Thomas L. Petty and colleagues initially identified acute respiratory distress syndrome (ARDS) [39]. ARDS is a clinical condition in which patient is chronically ill with acute respiratory failure, hypoxemia, and noncardiogenic pulmonary oedema [40]. ARDS is global public health concern and a type of respiratory failure that is life threatening [41]. In adults, the most common cases of ARDS include pneumonia (60 percent) or non-pulmonary sepsis (16 percent) [42][43]. For the development of this syndrome, pneumonia is the most common risk factor [44]. Depending on the degree of hypoxemia, the ARDS are divided into three ranges of severity; mild (PaO2/FiO2 200–300mm Hg), moderate (PaO2 / FiO2 100–200 mm Hg), and severe (PaO2 / FeO2 < 100 mm Hg) [45][44][46][47][48]. The basic characteristics of ARDS include formation of excess fluid in the lungs in existence of decreased pulmonary capillary wedge pressures (PCWP) [49]. There have been significant advances in the epidemiology, pathogenesis and pathophysiology of ARDS over the last 50 years [50].

ARDS affects about 3 million people each year globally, accounting for 10% of ICU admissions and 24% of ICU patients mechanically ventilated. ARDS mortality continues to rise, from 35% to 46%, with higher mortality correlated with higher levels of lung injury at first [51]. ARDS population-based estimates range from 10 to 86 cases per 100,000, with the highest recorded rates in Australia and the USA. In low-income countries where chest radiography and blood arterial gas measurement services are minimal, it is likely that ARDS remains unreported [52]. Many people living with ARDS, experience physical weakness, exhaustion, diminished quality of life and hospital discharge, and 12 months later may not be suitable for work. Despite advancements in ARDS management strategies, death rate is still extremely high [53]. There have been significant regional differences, such as the incidence of ARDS in Europe being 10-fold less than in the United States [54].

# COPD

The presence of poorly reversible airflow limitation is defined as chronic obstructive pulmonary disease (COPD) [55][56][57]. COPD is characterised by a related airflow obstruction, such as chronic cough, exertion dyspnea, expectoration, and wheezing [58–61]. It is closely correlated with tobacco smoking, but not all can develop COPD [62]. Although non-smokers can also develop COPD that tells us about other linked risk factor [63][64]. COPD rises as the world's third leading cause of human death after heart condition and stroke [65]. The global burden of COPD, sixth leading cause of death in 1990, fourth in 2000, is increasing worldwide, and estimated that it will be third by 2020 [66]. The United States ranks 12th in COPD mortality among 28 industrialised countries, while 7th in terms of women and men [67]. The primary cause of morbidity and mortality in high, middle and low-income countries is COPD. Data from WHO's Global Burden of Diseases and Risk Factor Project reveal that, COPD represented 3.8% of total deaths in 2001 and was the 5th leading cause of mortality in high income countries, and the sixth largest death cause in the low and middle- income countries, accounting for 4.9% of all deaths [68]. The World Health Report 2002 has classified COPD as the fifth-largest cause of death in the world, and its prevalence and mortality are anticipated to increase further in the next few decades [69][70]. COPD is a quiet murderer in low- and middle-income countries (LMICs): 328 million people around the world are estimated to be killed by COPD and COPD is predicted to become the lead cause of death in 15 years [71].

# Pulmonary Fibrosis

Pulmonary fibrosis is one field which is highly dependent on animal disease modelling. The most common type of interstitial pneumonia in men is idiopathic pulmonary fibrosis (IPF) [72]. IPF is a chronic life-threatening condition which is anatomically characterised by lung scarring and signs of activity dyspnea [73]. It is characterised in the presence of radiologically visible pulmonary infiltrates that primarily affect the lung foundations and the progressive dyspnea and weakening of the pulmonary function [74]. There are various etiologies of pulmonary fibrotic diseases, including allergens, toxic agents, radiation, and the atmosphere. However, it is still unknown what causes one of the most serious pulmonary fibrotic diseases, IPF [75]. We continue to enhance our awareness of pathogenesis of IPF. The initial model for the treatment of this condition, suggested three decades ago, indicated that the underlying cause for lung fibrosis was chronic inflammation [76]. The IPF is

confined to medium-aging and elderly adults and is associated with a histopathological or radiological form characteristic of the normal interstitial pneumonia [77,78]. The annual rate of IPF is rising, estimated at between 4.6 and 16.3 for every 100,000 individuals, with a prevalence of between 13 and 20 per 100,000 cases [79]. IPF has earned the most publicity among different types of interstitial lung disorder due to its uncommon poor prognosis and its lack of reaction to conventional therapies [80].

# COVID-19

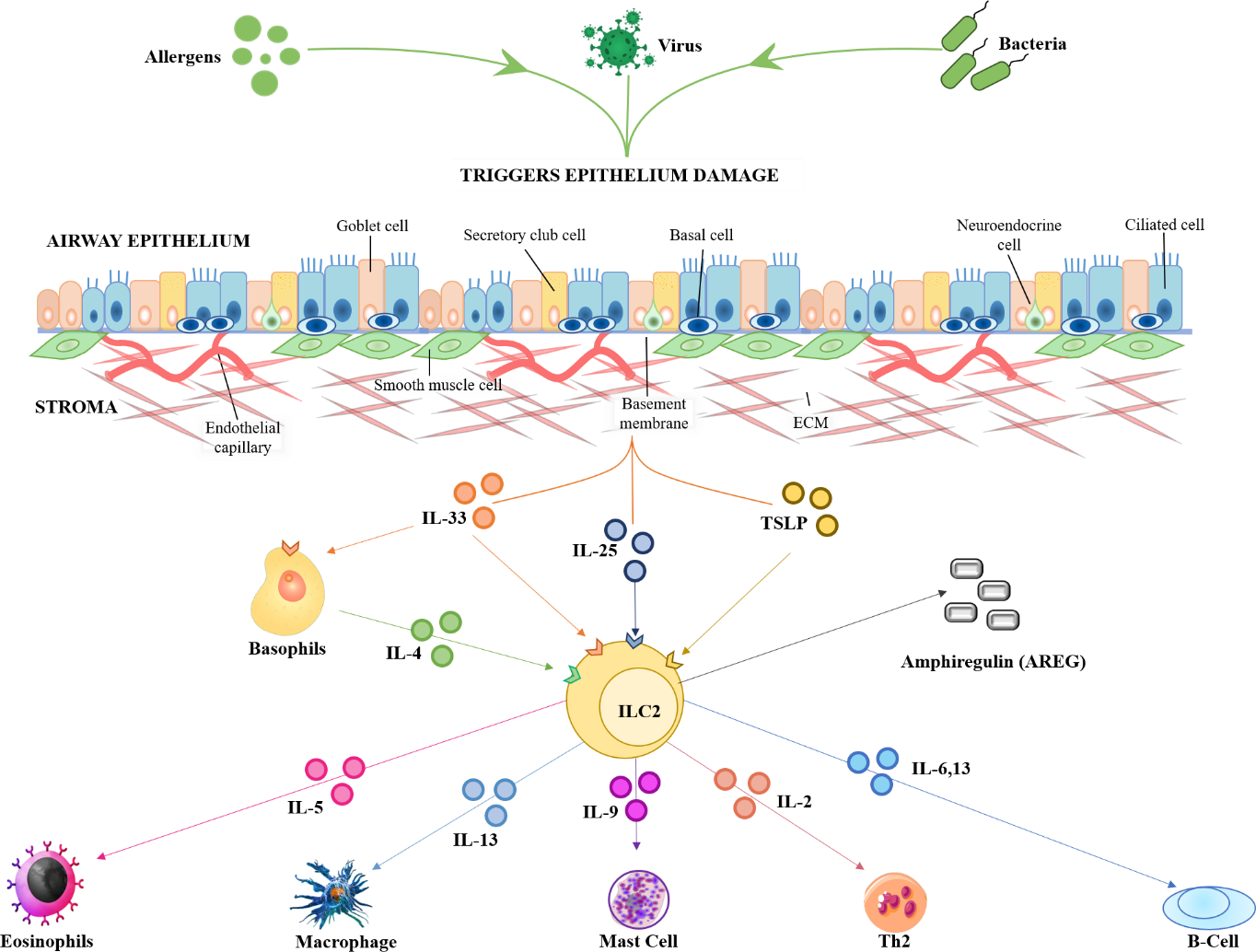
In 1968, the term "coronavirus" was derived from the electron microscopes because of corona-like or crown-like morphology of the virus [81,82]. In several species of animals, including humans, they cause acute and chronic diseases of the respiratory, enteric and central nervous system (CNS) [83].

The WHO named the novel Coronavirus Disease 2019 disease (COVID-19) on February 12, 2020, and stated it to be new pandemic disease [84][85]. The epicentre of this virus was claimed to be the Hubei province of the People's Republic of China, of SARSCoV-2 (Coronavirus 2019; formerly, 2019-nCoV), from where it has spreaded to several other countries [82,86]. At the onset of COVID-19, fever, cough, and fatigue are the most common symptoms, while sputum, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia was observed in few viral effected patients [87,88]. In combination of IgM, IgG with RT- PCR tests was developed for the identification of the unique SARS-COV-2, and was used for diagnosis in patients [89–91]. Moreover, person-to- person transmission in hospitals and families was illustrated by epidemiological evidence. The high COVID-19 infectivity has led to the robust growth of new cases and a global outbreak [92]. We ought to take notice that 81% of those diagnosed with COVID-19 have moderate illness and do not need hospitalisation as a result of their latest best estimates [93]. In Wuhan, a mortality rate of 5.0% was similar in worldwide (4.2%) to that of patients with COVID-19, and slightly higher than in mainland China, with the exception of Wuhan (2.4%) [94]. Globally, on 25 October 2020, there have been 42.7 million confirmed cases of COVID- 19, including 1.15 million deaths, reported to WHO.

# Interrelation between Interleukin and Respiratory Disease

Cytokine is a term used by a category of protein cell regulators known as interferons, lymphokines, and monokines formed by a broad spectrum of cells in the body, play an essential part in several physiological processes as well as in pathophysiology of various

diseases and have a medicinal application [95]. Cytokines are regulatory proteins that are secreted by white blood cells and various other cells in the body. Multiple functions of cytokines entail various effects on the immune system cells as well as inflammatory response regulation [96]. Cytokines are secreted proteins that control significant responses of cells such as proliferation and division of cells [97]. These are generated by numerous inflammatory cells including activated lymphocytes T helper 2 (Th2), mast cells, basophils and eosinophils [98]. Interleukins comprise a wide class of cell signalling molecules in the cytokine family. They were initially identified as leucocyte proteins. It has now become clear that they consist of various kinds of cells and interact with pleiotropic properties. Interleukins are often labelled separately, but often have several classes in their families. In total there are 37 interleukins and others with major chronic disorders of the airway [17]. Cytokines are often present at inflammatory sites during airway inflammation and can be a central component of epithelial disruption and the development of inflammatory reactions [99]. Cytokines such as interleukin i.e. IL-4, IL-5, and IL-13 are activated by subsequent T cell priming. These cytokines combine with their receptors in order to promote the development of IgE and to boost the number of eosinophils and mast cells, all of which are capable of exacerbating inflammation in the respiratory tract [100]. In the homeostasis of the body, cytokines and their receptors play a role; therefore, manipulating maybe one of them may control not only the pathological mechanism of concern but also other indirect pathways with potentially harmful consequences. Moreover, Security and tolerability are also the undeniable issues. Troubling. The **Figure 2** illustrates the inter-relation between different CRDs and ILs [101].



**Figure-2:** Diagrammatic representation of inter-relation between interleukins and respiratory diseases

Asthma is an airway obstruction that contributes to reversible airway blockages by a number of "stimuli" [102]. The epithelium shows structural disruption in asthma and hyperplasia and metaplasia of the mucus cells [103]. In the growth of airway inflammation, mucus formation, and respiratory hyperresponsiveness among asthma patients, interleukin-4 and interleukin-13 are found to play vital role. In the pathogenesis of atopy and atopic asthma, interleukins (IL)-4, interleukins (IL-5 and IL-13) are the essential cytokines that have been expressed by type-2 (Th2) cells [104][105]. Both IL-4 and IL-13 facilitate a variety of cell types of acute inflammatory processes and the structural modifications in airways underlies their receptors [106]. The association between IL-4, IL-13 and asthma has been demonstrated in several studies [105]. IL-4 activates B cells to produce Type E (IgE) immunoglobulin and facilitates Th2 cell proliferation and the development of cytokine. On the other hand, IL-5 is involved in eosinophil's activation, differentiation, growth, migration, proliferation, and survival. Whereas, IL-13 has a broad variety of functions, including mucus hypersecretion

and cell metaplasia, stress control that influence airway muscle smooth contraction and relaxation, ASM proliferation and airway respiratory hyperresponsiveness [107][108]. There are now known signals of IL-4 and IL-13 to trigger two separate IL-4 receptor complexes i.e., Type I and Type II. Type I receptor is composed of IL-4Ra and ᵞc subunits, located predominantly on the hematopoietic cells, and binds IL-4 exclusively, with Janus kinase 1 and Janus kinase 3 (JAK1 and JAK3). Type II is composed of IL-4Ra (IL-13Ra1) and thus associated with both the IL-4 and IL-13 and then activates the Tyrosine kinase 2 (TYK2) and JAK1 receptors, which are mainly located in non-hematopoietic cells [109]. When IL 4 or IL- 13 binds to IL-4Ra, smooth muscle airway cells release chemokine eotaxin, which is used to specifically chemoattract eosinophils [107][110][111].

ARDS can be linked with several clinical disorders that can be broken into those associated with direct lung injury and those associated with indirect lung injury in a systemic process environment [112]. ARDS is known to trigger an extreme pro-inflammatory and anti- inflammatory reaction in the lungs, as several studies have shown [113]. The tumour necrosis factor α (TNF-α), interleukin 1β (IL-1β), IL-6, and IL-8 are two of the most important early reaction cytokines. All are present in patients at risk for ARDS and with proven ARDS in the bronchoalveolar lavage fluid (BALF) [114][115].

COPD is "avoidable and treatable condition, characterized by persistent airflow obstruction, which is typically progressive and correlated with higher chronic inflammatory response in the airways", according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease [116]. In addition to the factors of growth such as transforming growth factor (TGF)-β), cytokines and chemokines that can affect the COPD include tumour necrosis factor(TNF)-α, interleukin(IL)-1β, IL-4 , IL-5, IL-6 , IL-8 (CXCL8), IL-13, IL-17, IL-18, IL-

23, IL-33, and thymic stromal lymphopoietin(TSLP) [117][118][119]. In the inflammatory mechanism of COPD, many inflammatory cells and mediators participate [120,121]. They can inhibit the inflammatory process which is susceptible to maintaining the progressive form to COPD [122].

IPF is a recurrent and persistent fibrosis of the uncertain aetiology that results in death triggered by respiratory failure [123][124]. Study in both animal and human models of pulmonary fibrosis has shown that different cytokines are produced locally in these systems,

and these cytokines are thought to be involved in different steps in pulmonary fibrosis pathogenesis [125]. One present theory concerning the key pathogens for pulmonary fibrosis includes the difference of pro- and anti-fibrotic/inflammatory cytokines and growth factors like the tumour necrosis factor (TNF)-α, TGF-β, interleukin 1 (IL-1)Rα and IL-6 [126][127][128][129].

Coronavirus outbreak 2019 (COVID-19) was first recorded in China in Wuhan, where it was reported first then quickly spread worldwide, caused by acute respiratory syndrome Coronavirus 2 (SARS-Co V- 2) [130][131]. COVID-19 infection is followed by an intense inflammatory response in an incident termed a "cytokine storm" with the release of a large volume of pro-inflammatory cytokines. The host SARS-CoV-2 immune response is hyperactive and contributes to an extremely inflammatory reaction [132]. The virus causes a cytokine storm by releasing multiple pro-inflammatory mediators such as interleukin-2 (IL- 2), IL-6, IL-7 and tumour necrosis factor-alpha (TNFα) [133][134][135]. A reported research with 40 patients of COVID-19 (13 of whom are severe) indicates that a persistent decline in their lymphocyte amounts associated with mild cases exists in severe cases. In severe cases, the decreasing in CD8 + T-cells and inflammatory cytokines [IL-6, IL-10, IL-2 and interferon-gamma (IFN μ)] increased in the peripheral blood [136].

# Current Treatments Available for treating Chronic Respiratory Disease

* 1. **Antibiotics**

Conventional administration of the medication means that the medication is formulated as a suitable shape, such as tablet or intravenous solution. Antibiotics are the foundation of infectious disease medicine and have been used for over 50 years. The Webster Third International Dictionary (1981) describes an antibiotic as "a product made by a micro- organism (such as a bacterium or fungus) which have the power either to suppress the growth or kill another micro-organism (such as germs) in dilute solution [137]. In respiratory conditions such as asthma and COPD, antibiotics are widely used [138]. Infection caused by bacteria (40-60 percent), viruses (approximately 30%) and atypical bacteria (5-10 percent) are common cause for COPD exacerbations [139][140]. Problems with the oral antibiotics prompted scientists, through inhaled, aerosolized or nebulized antibiotics, to supply antibiotics through the pulmonary system. Inhaled antibiotics were used for many decades to treat respiratory tract infections [141]. The main goal of CRD's patients care is to

reduce and successful management of exacerbations. Antibiotic treatment can help patients with increased production of sputum, combined with purulence and deteriorating breathability [142][143]. Although, this approach is effective to combat the complications imposed by the CRDs, but long-term usage of these antibiotics has its own adverse effects which varies with concomitant comorbid conditions and drug type. Moreover, the long-term usage of different drugs also obstructs the proper functioning of immune system [144]. In few cases, long-term exposure of drug in body leads to development of significant symptoms of gastrointestinal infection like abdominal cramps, diarrhoea, dyspepsia, vomiting and nausea. Moreover, there extensive usage often led to the development of antibiotic resistance in the body, which makes the antibiotics less effective [145].

# Corticosteroids

Corticosteroids are commonly used for the treatment of different inflammatory and immune disorders. The primary use today of corticosteroids is in asthma therapy, and first line of therapy in adults and children with chronic asthma have been established through inhaled corticosteroids [146]. In the last 20 years, both oral (prednisone, prednisolone) and inhaled (Fluticasone, Budesonide) corticosteroids play a significant role in asthma and COPD care [147–151]. Alsaeedi et al., 2002 reports indicate that inhaled corticosteroids promote COPD reports in terms of outcomes in patients. Regular use of inhaled corticosteroids in the doses used by these studies decreased almost one third the likelihood of intensification and the overall exacerbation incidence [152]. While inhaled corticosteroids are highly beneficial in asthma, they provide comparatively little effect in COPD [59]. There are increasing evidence showing that corticosteroids can decrease systemic and local inflammation and provide a possible therapeutic benefit mechanism in COPD [153]. Generally, corticosteroids have two beneficial acts in COPD: they can shut off inflammatory gene transcription and modulate the activity of β2-adrenoceptor [154]. Given the limited therapeutic range and severe side effects profile, the systemic corticosteroids are the most effective but not specific anti-inflammatory medications currently used [155]. Regardless of the benefit, corticosteroids therapy also imposes significant adverse effects on the patient health. The toxicity induced by the steroid therapy is stated to be the reason of morbidity [156]. As most major CRDs patients are on immunosuppressive therapy along with other toxic medicines leads to cumulative toxicity. In few cases, the adverse effects of corticosteroids remain hidden until major complication arises [157]. For example, reduced density of bone remains unchecked

till the patient encounters vertebral collapse. The long-term usage of corticosteroid is also claimed to cause cataracts, dermal atrophy, development of glaucoma, elevated intraocular pressure purpura and skin thinning [158].

# Bronchodilators

One big consideration in the treatment of respiratory conditions such as asthma and COPD are the use of bronchodilators. Bronchodilators acts by relaxing steady muscle tone, leading to reduced activity of respiratory muscles and progress in the mechanisms of ventilation [159][160]. There are three types of bronchodilators widely used alone or in conjunction: anti-muscarinic agents (Tiotropium), methylxanthines (theophylline), and β2- adrenoreceptor agonists (albuterol, pirbuterol, terbutaline, salmeterol, formoterol) [161]. Airflow reduction by raising airway diameter via direct action on airway smooth muscle, β2- Agonists minimise airflow obstruction.

Tiotropium bromide (Muscarinic Antagonists) is clinically successful in COPD treatment by enhancing baseline FEV1, reducing the incidence of exacerbations and improving the quality of life [162]. The present management of COPD is focused on inhaled bronchodilators. The use of short-acting bronchodilators is prescribed as a drug to relief from the symptoms, whereas long-acting inhalation bronchodilators are choice of medication for the management therapy [163][164]. Inhaled bronchodilators are the mainstay for asthma and COPD patients as monotherapy or in combination [165]. The long-acting inhaled bronchodilators commonly active are the once- daily anticholinergic tiotropium and the long-acting twice-daily β2 agonists, formoterol and salmeterol [166]. Even though the use of bronchodilators is effective but adverse effects arises on the activation of sympathetic system. The over usage of bronchodilators is also known for developing of side-effects like abdominal pain, problem during sleeping, muscle cramps, nervousness, high palpitations. In severe cases, side effects involves hypokalaemia, constricted bronchial airway and paradoxical bronchospasm, whereas in very rare cases it can also lead to myocardial infarction [162].

# Challenges associated with Conventional Treatment for treating Chronic Respiratory Disease

There are a range of drawbacks to traditional dosage forms: several doses are necessary to retain an optimal dosage level, regular dosing is needed for drugs with a limited half-life, lower effectiveness, adverse effects, and, can trigger a reduction in patient compliance, is

seen in typical dosage formulations that give rise to hindrance in retaining optimal drug concentration [167].

The long-term use of antibiotics may be characterized by the following important types of adverse effects: cardiac toxicity, ototoxicity, nephrotoxicity, and drug-drug interactions [168][169]. The IV use of wide-spectrum antibiotics also disrupts normal flora of the gut and raises risk of secondary diseases, and may encourage the resistance of drug [170].

Adrenal abnormality, dermal thinning, diabetes, elevated blood pressure, hyperadrenocorticism, infection, osteoporosis, paranoia, peptic ulceration, and formation of cataract has been linked with the use of corticosteroids [171][172][173][174]. Specifically, systemic corticosteroids may trigger some severe adverse effects [175]. As corticosteroids maintain some mineralocorticoid activity (prednisone and prednisolone), they improve distal reabsorption of the sodium renal tubules in exchange for Potassium, ammonium and hydrogen ions in certain people, which may induce hypernatremia and hypokalaemia [176].

Inhaled corticosteroid (ICS) use in patients with respiratory disease is linked to a moderate raise in the risk of developing diabetes and advancing diabetes [177]. There was doubt that osteoporosis could be caused by the long-term use of inhaled corticosteroids. In a population-based case-control analysis, Ernst and colleagues demonstrated that ICS use in COPD was related to an increased pneumonia risk. Many studies have shown that long-term application of ICS enhances skin bruising [178]. The incidence of oropharyngeal candidiasis and bruising of skin increased by the use of inhaled corticosteroids [152].

The side effects of short acting β2 agonist includes increased plasma glucose, reduced serum Potassium, tachycardia, and tremor [179]. In all of the studies analysed, tiotropium was associated with a higher frequency dry mouth. Formoterol in one study tended to be related to elevated tachycardia and tremor. The increasing occurrence of adverse effects associated with the ear, nose and throat was linked to Salmeterol [180]. Side effects of ipratropium include mouth dryness and poor taste complaints [181].

# Advantage of Novel Drug Delivery System

Targeted and modified drug delivery systems were designed to resolve the shortcomings of traditional dosage forms. This was the moment when there was a strong demand for a novel drug delivery system (NDDS) [182]. In recent decades, search for the effective and safe therapy led the development of a novel drug delivery system and has gained significant attention [183]. Dendrimers, ethosomes, liposomes, microspheres, nanoemulsions, nanoparticles, niosomes, phytosoms, stable lipid nanoparticles, trans-dermal drug delivery systems, and so on are some recent development in the delivery of the drug. All the listed drug delivery systems are highly advanced and have a capacity to carry the drug formulation to the defined target location and even improve its functionality when the active compound reaches the body [184].

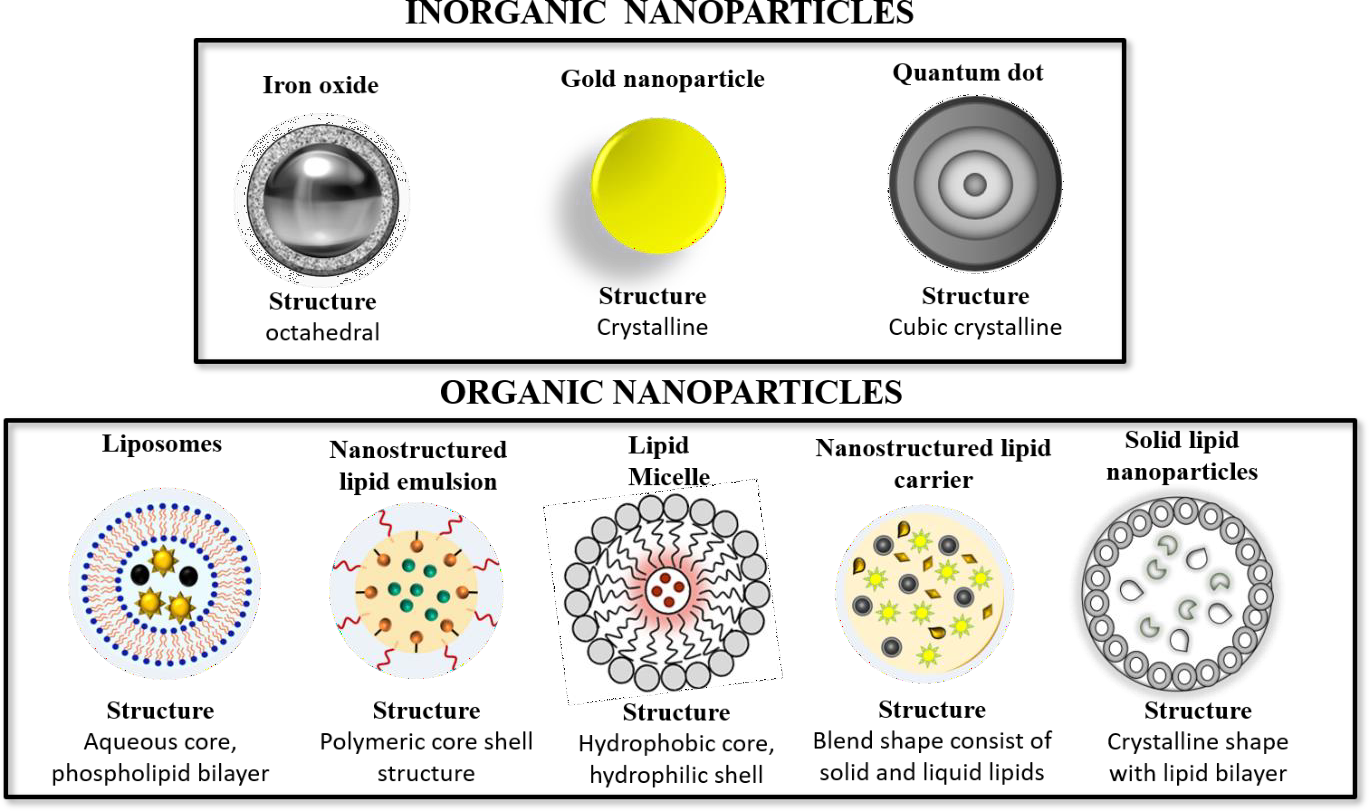
At the end of the 1960s, Prof. Speiser created the first nanoparticles for drug delivery for tetanus, diphtheria and other infections at the Swiss Federal Institute of Technology in Zurich. Currently, further development in nanomedicine is very promising for the long-term release and distribution of various therapeutic agents [185]. Colloidal arrays with particles ranging from 10 nm to 1000 nm are nanoparticles. The literature has also reported in nanoparticle systems with average particle size well over the 100 nm standard [186]. NDDS have many benefits over traditional multi-dose medication, such as effective means of precisely supplying the drug to the intended site, Optimum concentration of the drug in the blood for extended period of time, decreased of frequent dosing, better compliance, and, maintaining the intended concentrations at the targeted site without harm [187][188]. NDDS is a breakthrough system for the delivery of drug that enhances potency of drug, tracks the release of drugs to produce a continued therapeutic efficacy, improves drug pharmacology and enhances safety; and finally, targets at a particular drug tissue. There are different NDDS, which includes: Implant Drug Delivery Systems, Nasal and Parenteral and Pulmonary Drug Delivery, Oral Delivery Drug Delivery Systems, Transdermal and Topical Drug Delivery, Transmucosal Drug Delivery [189]. Here we listed the few advantages of NDDS [190]:

1. Increasing the solubility.
2. Enhanced bioavailability.
3. Toxicity safeguards.
4. Increasing the pharmacological activity.
5. Stability development.
6. Enhanced dispersion of tissue macrophages.
7. Sustained delivery.
8. Physical and chemical degradation safety.

# Novel Drug Delivery System for Treating Chronic Respiratory Disease

New systems of drug delivery are the latest innovations in understanding the pharmacokinetic and pharmacodynamic behaviour of drugs that provide the production of the optimum drug supply mechanism for a more rational approach [191]. Nanotechnology is a field that integrates the medication into a nanosystem that offers new pharmacotherapy dimension and a cell-based approach for drug delivery [192]. With several possible uses in clinical medicine and science, nanotechnology offers new materials in the nanometer scale. Nanomaterials such as nanoparticles provide the ability to create both new therapeutic and diagnostic instruments due to their unique size-dependent properties [193].

Specific organic or inorganic ingredients are currently used in the preparation of nanoparticles, such as lipids, collagen, metals, and natural/synthetic polymers. Based on size, morphology, chemical and physical properties, nanoparticles may be categorised in various groups. Some among them are carbon nanoparticles, ceramic nanoparticles, metal nanoparticles, nanoparticles for semiconductors, polymer nanoparticles and lipids nanoparticles **Figure-3** [194][195].



**Figure-3:** Diagrammatic representation of various Nanoparticles for drug delivery system

# Organic Nanoparticles

**Interesting features of nanoparticles have drawn broad interest to numerous medicinal uses, including the detection of illnesses, the delivery of drugs, bioimagery and treatment for many diseases. There have been major efforts to establish different techniques to create organic nanoparticles with different morphologies and properties [196].**

The purpose of the development of solid lipid nanoparticles (SLNs) in 1991 is to provide biocompatibility, storage stability and prevent degradation of the integrated medicinal substance. SLNs, nanoscopic (50–1000 nm) colloidal carriers consisting of solid lipids are designed to resolve flaws in the conventional colloidal carriers such as polymer nanoparticles and liposomes [197]. SLNs are distribution systems based on lipids with a range of advantages over other nano delivery systems including bypassing spleen or liver filtration of 120–200 nm particulate size, lower chronic or acute physiological lipid toxicity, improved bioavailability and efficiency, improved repetitiveness and decreased use of organic solvents in preparation [198]. SLN's incorporate the benefits of polymer nanoparticles, fat emulsions and liposomes while avoiding their drawbacks at the same period [199].

Polymer NP's have many benefits, including the enhanced surface properties and high drug capsulation, shield the medications from deterioration, and, extended delivery of drug and long shelf-life, these are promising carriers of biological agents [200]. The most widely used polymers for treatment are poly (Lactic acid) (PLA), poly (Lactic-co-glycolic acid) (PLGA), poly (ε-caprolactone) (PCL), alginate, chitosan and gelatin base [201]. For the treatment of chronic respiratory disorders like asthma and COPD, a number of polymer nanoparticles have been developed [27]. To control asthmatic inflammation,

Dendrimers are composed of tree-like limbs or limbs, with an even and uniform shape, which have enhanced physical-chemical features in contrast to conventional macromolecules. Dendrimers are extremely monodispersed nanoparticles, and the final composition is precisely controllable in size and in surface function [202]. Dendrimers are nano-sized and radially symmetric, artificial, well-defined macromolecules that have a mixture of a variety of functional and compact molecular structures [203].

# Inorganic Nanoparticles

For over a century, nanoparticles have been fascinated by scientists and are commonly used in biomedical and engineering sciences. These products are now available for synthesis and modification of various chemical groups to be paired with antibodies, ligands and medicines of interest to open up a variety of possible applications in biotechnology, magnetic isolation, target research, tailored pharmaceuticals and medicines, and most specifically, identification of gene and drug delivery vehicles [204]. Nanoparticles were often built using inorganic materials like gold, iron oxide and silica. Inorganic material creates imaging contrast by computed tomography (CT), magnetic resonance resonance (MR) or positron emission tomography (PET) depending on the special plasmonic and magnetic properties [27].

The ferrimagnetic-class nanoparticles of iron oxide are used for many different biotechnological and biomedical applications. Magnetite (Fe3O4), maghemite (γ-Fe2O3) and hematite (α-Fe2O3) are among the numerous forms of iron oxide-based nanoparticles [205]. In general, the use of iron oxides in many biological processes is expanding and is very cheap. Their low toxicity has drawn a lot of attention and is particularly interesting in biomedical applications for protein immobilisation, such as Magnet Resonance Imaging (MRI), thermal therapy and medical distribution of pharmaceutical products as well as

superparamagnetic characteristics, such as surface and volume ratio and the easy separation technique [206].

Inorganic nanoparticles have demonstrated little effectiveness in the treatment of chronic respiratory disease. For example Exposure to TiO2 nanoparticles dramatically enhanced the production of reactive oxygen species and lipid peroxidation, and lowered antioxidant capacity in the lung. Moreover, TiO2 NPs exposure activated NFkB and raised levels of cytokines such as TNF-α, IL-2, IL-4, IL-6, IL-8 and IL-10 [207]. Nounou et al. found that oral administration of ZnO nanoparticles caused lung injury in rats via oxidative stress, inflammatory response, and DNA damage [208].

Gold nanoparticles have been successfully supplied in a COPD mouse model to the alveolar epithelial cells [209]. Because of its strong antimicrobial activity against bacteria, virus and other microorganisms, silver nanoparticles have been most efficient. In immunochemical experiments, gold nanoparticles (AuNPs) are used to classify protein interactions. They are used for the identification of DNA presence in a sample as a laboratory tracer [210]. Gold NPs may also improve Raman scattering on the surface of the NP to detect and identify biomolecules [211].

Quantum dots (QDs) are thin, semi-conducting substance nanocrystals of 2 to 10 nm in diameter. This particle is composed of an inorganic semiconductive core like CdSe and an organic aqueous filled shell like ZnS. QDs emit distinctive colours of fluorescence, in part due to an extremely high surface/volume ratio for certain particles [212]. The core structure of QDs determine the colour emitted and are widely used as fluorescence imaging tools for cell labelling and biomolecule tracking in biological research [211]. A study by Kalangi et al. conjugate celecoxib and quantum dots. The mice's inflamed paw was targeted by these quantum dots-celecoxib conjugates, which not only had an accurate anti-inflammatory effect but also a bio-imaging effect [213]. In an *in-vitro* experiment, Kumar et al. combined sodium 10-amino-2-methoxyundecanoate (SAM) with N-doped graphene quantum dots (N-GQDs). In comparison to cells treated with SAM alone, SAM combined with N-GQDs enhanced inhibition of COX-2, iNOS, TNF-, NF-ß, IL-1, IL-1ß, IL-4, and IL-6 [214].

Wang et al. developed PEG5000- PLGA NPs loaded with Bavachinin to supply bavachinin orally to cure asthma. These NPs were highly biocompatible with the inflamed lung tissues and demonstrated a specific targeting capability. These NPs demonstrated very strong therapeutical anti-asthmatic effects through oral administration of a murine allergic asthma model tested with histological section review, local and systemic cytokine expression and T-cell differentiation. In the peripheral blood of these mice, ELISA observation has also shown a clearly modulated cytokine Th1 / Th2, in which IL-4 expression is efficiently suppressed and the IFN-ᵞ is moderately high. The study of RT-PCR also found that local Th1/Th2 cytokines were modulated in the lung tissue by the mRNA levels [215].

The biocompatibility of the PEGylated dextrane-coated SIPON combined anti-Il4Rα, and its efficient binding and proper aiming to IL4Rα have recently been documented by Halwani et al in 2016. Currently, several superparamagnetic iron oxide nanoparticles (SPIONs) have been approved for early clinical or experimental studies and for clinical use in medical imaging and therapeutic applications several formulations. IL4Rα may offer a new therapeutic model of the biological compound, particularly for those suffering from uncontrolled, severe asthma [216]. Faraj and his team prepared an antibody-conjugated, polymer-coated nanoparticle system that inhibits the inflammatory pathway triggered by the immune system's interleukin-4 receptor α (IL4Rα). These anti- IL4Rα nanoparticles reduced proinflammatory cytokine release and the number of inflammatory cells in lung tissue and BALF. Furthermore, anti- IL4Rα nanoparticles reduced CD4+ and CD8+ T cell activity in lung tissue while inhibiting their ability to release proinflammatory cytokines more effectively than the free antibody .

In its research, Silva et al., 2014 found that a single administration of thymulin plasmid- containing DNA nanoparticles, but not plasma alone, significantly enhanced IFN-γ which is known to inject the role of Th2 mediated effectors by stimulating Th1 cells [217].

Quercetin encapsulated liquid crystalline nanoparticles (LCNs) decreased pro-inflammatory mediators including IL-1β, IL-6 and IL-8 effectively and further increased its anti- inflammatory activity by encapsulating quercetin into LCNs. This indicates that quercetin LCNs might be used for the treatment of asthma as a possible new drug delivery [218].

Another study showed that celastrol loaded liquid crystalline nanoparticles reduce IL-1β production thereby helps in alleviating the symptoms of asthma [219].

Zhang et al., found that apigenin-NPs can arrest cell cycle and inhibit proliferation at higher doses during phase G0/G1. These findings indicate that apigenin-NP can be used for IPF by suppressing rapid fibroblast proliferation that leads to scar progression in lungs and without the death of the pulmonary cells at the same time. Their analysis showed an increase of TNFα, IL-8 and IL-6 mRNA mediated inflammation in the rat IPF model. We found that apigenin can decrease both IL-8 and TNFα according to previous studies [220].

Kenyon et al. found that systemically administered dexamethasone encapsulated in self- assembling nanoparticles (Dex-NP) decreased allergic lung inflammation and airway hyper- responsiveness in asthmatic mice to a larger degree than equal dosages of dexamethasone alone. According to study findings, when OVA-exposed mice were treated with Dex-NP, the number of total cells and eosinophils in their lung lavage was much lower than when they were just exposed to OVA without Dex-NP. Interleukin-4 (IL-4) and monocyte chemotactic protein-1 (MCP-1) were shown to be reduced in the lungs of the Dex-NP group when compared to the control group [221].

# Concluding Remarks and Future Prospects

In particular because of the population's ageing and the lack of appropriate steps to eliminate risks associated with emergence/persistence of these diseases, the CRD 's burden is immense and becoming ever more widespread globally. In comparison, there is a shortage of successful therapies to cure and/or stop these severe respiratory conditions that can possibly be used. As well as more studies into the development of alternative therapies for CRDs, steps should be taken to ensure that medications at the pathological site, i.e. airway epithelium, parenchyma and bronchioles, are administered optimally. In addition, particular cell types which could play a key role in the development of diseases should be targeted for treating. The application of NDDS on ILs include new treatments that will be of considerable significance in potential care of CRDs.

Nanotechnology has evolved exponentially in recent decades for drug delivery systems. Recent technological advancements in medicine have created a clear potential for the

treatment of chronic respiratory diseases by selective therapy using nanoparticles. NDDS are developed with a diverse range of applications and have shown promising results in treating diseases with more safety, efficacy, and precision. Many of the clinical approaches involving NDDS not only regulates the indented pattern of drug level within the blood, but also aids in targeting the drugs to a specific site or site of action. As a result, it circumvents the dose- associated toxicity and side effects.

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**Highlights**

* + Nanotechnology provides novel strategies in clinical treatment of respiratory disorders
  + Airway defenses is strengthened by sustained release of drugs
  + Nanocarriers can also be used for combination treatment of drugs targeting interleukins

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

* The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: