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# Current challenges and future scope of nanoparticles in chronic obstructive pulmonary disease

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**Abstract:**

Chronic obstructive pulmonary disease (COPD), characterized by airway inflammation and progressive airflow limitation, is one of the leading causes of mortality worldwide. Bronchodilators, corticosteroids, or antibiotics are used for treatment of COPD, but the drugs are not delivered properly to the target cells or a tissue, which remains a challenge. Nanoparticles (NPs) have gained a tremendous interest in respiratory medicine due to their smaller size, higher surface to volume ratio, and advantages such as targeting effects, patient compliance, and improved pharmacotherapy. Sustained delivery of drugs mediated by NPs to the targeted site is needed to control cell chemotaxis, fibrosis, and chronic obstruction of lungs in COPD. Development of multifunctional biodegradable NPs that are nontoxic and can help in overcoming airway defense will be beneficial in future for COPD.

**Keywords:**

COPD, drugs, nanoparticles

## Introduction

Chronic obstructive pulmonary disease (COPD), a progressive lung disease characterized by pulmonary and systemic inflammation, has become a major and increasing global health problem. This chronic airflow limitation is either due to small airway disease or destruction of parenchyma[1] and reduced elastic recoil,[2] and both progressively lead to trapping of gas while expiration thereby causing hyperinflation. Cigarette smoke and infection further induces this inflammation in airways. For symptomatic management of COPD, medicines such as bronchodilator are in use. The bronchodilators such as ß$_2$-agonists, anticholinergics, and methylxanthines are used either alone or in combination. Inhaled Corticosteroids are also effective in patients as by their use improvement is observed in symptoms, lung function, etc., but long-term monotherapy is not recommended. Chronic inflammation during inflammatory conditions is controlled either by using corticosteroids, antibiotics or bronchodilators, but despite therapy, the drug is not delivered properly to the target cells or a tissue, which remains a challenge. Inhaled corticosteroids helps in delivery of the drug directly to the lungs providing quick relief, but as particles

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produced by these are large, most of the drug gets deposited in the upper respiratory tract, thereby limiting their effects. Development of drug using biodegradable nanoparticles (NPs) can directly reach to the desired site and overcome airway obstruction and other associated challenges in the treatment of chronic pathophysiology of obstructive lung diseases.[3]

NPs have gained immense interest in pharmaceutical industry particularly in respiratory medicine due to their smaller size (diameter ranging from 1 to 1000 nm), high surface to volume ratio, targeting effects, and improved pharmacotherapy.[4] They can be prepared either from natural polymers (such as protein and polysaccharide) or synthetic polymers (such as polystyrene). Preparation of NPs from natural polymers involves simpler methods while that prepared from synthetic polymers involves the use of organic solvent, heat, and high shear force that harm the stability of a drug.[5] NPs include nanospheres, nanocapsules, liposomes, dendrimers, polymeric NPs, and solid lipid NPs. Biological properties of nanocarriers can be changed and controlled as per requirement thereby making them of great use in therapeutics.[6] The ability of NPs to act on particular targeted site depends on many factors such as size of the particle, its surface charge, and hydrophobicity. Cell-specific targeting and penetration of drug at précised location are necessary as delivery of drugs to the specific site will have a good effect. Low dosage use will also reduce undesirable side effects. Current research in the field of nanomedicine or the delivery of drug at targeted site using NPs has these benefits due to their properties of tissue penetration, efficient delivery, and accumulation of drug in the affected area.[7,8] Drugs given systemically are effective but sometimes have adverse reactions[9] while in drugs which are tagged with nanocarriers, there is relatively uniform distribution within the alveolar surface; so, its solubility increases and release is prolonged resulting in reduction of frequency of drug administration, improved patient compliance, and least side effects.[10]

Severe inflammation, airway defense, and mucous hypersecretion in COPD patients are the barriers in path of proper drug delivery and drug efficacy.[11,12] Sustained delivery of drugs mediated by NPs to the targeted site is needed to control cell chemotaxis, fibrosis, and chronic obstruction of lungs in COPD.[3]

The breakdown properties and diffusion characteristics of the NPs at the targeted site are necessary for good therapeutic effect.[13] NPs are of different types such as quantum dots, lanthanide, silica, or metal NPs, and as all are having unique properties, they are used for different purposes in the bioanalytical field.[14-19] Quantum dots are used in biological research as drug carriers or fluorescent labels for discovery of drug or detection of disease[15,16] while polymeric NPs may also offer a new advancement in drug discovery.

Lipid-based NPs are also used nowadays as they are formed from biocompatible lipids, and moreover, lipophilic drugs can be easily incorporated in its membrane through their help which limits their toxicity.[20] As these NPs are aerosolized, their uptake is easy, and due to their longer retention period in lungs, they are of good use.[21] For the treatment of COPD, $TiO_2$ and carbon black (CB) NPs could be promising metallic nanocarriers.[22] Having surface plasmons resonanance, Gold, Silver and Copper NPs are also in great use. Gold NPs are of good choice for précised targeting of alveolar epithelial cells and macrophages in COPD.[23] Using supercritical fluids for production of NPs is promising as it is environment friendly and has no toxicity.[24] The antioxidant Nrf2 activator is used as a single-component dry spray for delivery of drug to targeted site. As they are aerosolized, these particles can reach the lower airways and be used in the treatment of inflammation occurring in diseases such as COPD.[25]

Currently, a development of multifunctional polymeric vesicle formed by a mixture of poly (ethylene glycol)-poly (lactic-co-glycolic acid) is underprocess for delivering of COPD drugs and molecular probes in combination to the targeted site. In future, observing the biodistribution and effects of the PROBE/DRUG-loaded nanocarriers in real time will be helpful in personalized and precision medicine approach in COPD[3] Another emerging area for nanotechnology lies in stem cell-based therapies. Mesenchymal stem cells infusions have demonstrated safety in COPD, associated with a decrease in serum C-reactive protein level and without improvement in lung functions but has provided the basis for future research.[26] Metallic NPs are also used effectively for delivery of drug as they can penetrate in cells and tissues easily; but, however, these NPs have toxic effects.[27]

To overcome the hurdles in the field of nanotechnology, lot of research is going on to establish nanoparticle-based drug delivery as the gold standard for site-specific therapeutics.[24] Recent advances in nanotechnology are helpful in delivering the drug to the specific site and preventing severe adverse side effects. By modifying size, shape, surface charge, and surface properties of nanoparticle, their efficiency can be maximized and their deposition in the lung can be prevented.[28,29] Concerns have been raised toward widespread use of NPs due to their toxic effects. Along with several benefits, NPs too poses several potential risks. There is an immense need for safety evaluation of NPs as they may have adverse effects on the body such as fibrosis, inflammation, or genotoxicity. Inhalation is the primary route for entry of NPs into human bodies. When inhaled NPs remain in the lung, they may impair or prolong alveolar macrophage-mediated clearance function

continuously and interact with the pulmonary epithelial cells. This may result in subsequent lung injury.[30] Previous studies in animal models have shown that inhalation of NPs may cause lung injury which in later periods may develop into any respiratory disease such as COPD, asthma, and even lung cancer.[31-33] Studies in human population also show that ultrafine particles in the air are also a risk factor for many respiratory diseases. Occupational exposure to different NPs has been associated with inflammation in the lungs and pleural effusion.[34,35] Polyamidoamine, that is used in drug delivery, can induce autophagic cell death, and many other types of nanomaterials such as silica, CB, and metal oxides can induce inflammation or fibrosis in lungs.[36,37] Exposure of polyacrylate NPs to workers in a print plant has been seen to lead to a nonspecific pulmonary inflammation and pulmonary fibrosis in the lung tissue which raises the concern that longterm exposure of NPs without protective measures may damage lungs.[38]

Since inhalation is the most important treatment modality in COPD, the benefit and harm ratio should be considered in the use of NPs in COPD drugs. Research is going on how to reduce these effects either by changing their chemical structure or incorporating metal oxide-based antioxidants.[28,39] As these NPs can overcome the mucus and lung remodeling barriers, they will be helpful for respiratory diseases in near future.[38] Development of multifunctional NPs that can serve the purpose of both diagnostic and therapeutic will be beneficial in the field of drug delivery and diagnosis of disease and its treatment.

## Conclusion

Nanoparticles play a vital role in medical research by delivering improvements in diagnosis of disease and its monitoring. It is also making significant impact in field of regenerative medicine and drug delivery. NPs if designed properly taking care of its target location, route of administration, side effects, etc., will be very helpful in the world of research and therapeutics innovation. Future research on multifunctional biodegradable NPs that are nontoxic and can help in overcoming airway defense in COPD will be beneficial for diagnostic and therapeutic purposes.

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### Conflicts of interest
There are no conflicts of interest.

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