REVIEW ARTICLE

Applications of Nanoparticles in Treatment of Respiratory Disorders

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ABSTRACT

Respiratory disorders are very prevalent and high-incidence group of diseases having severe impacts on human health in the world. Some of the respiratory disorders are difficult to diagnose and treat, such as chronic obstructive pulmonary disease, asthma, lungs cancer, and pulmonary tuberculosis. Lungs cancer is the second most common cancer globally. Nano-delivery technologies have a great potential to improve the drug targeting in a specific area of infections in respiratory disease treatment. Not only nanoparticles concentrate the drug at specific-disease sites but also reduce the drug degradation and drug loss simultaneously. Sedimentation, nebulizers, carbon nanodots, and stimulus-responsive nanoparticles are currently being explored to use as a source for delivering nanodrugs to treat lungs cancer. Various nanoparticles such as steroids, salbutamol, liposome-mediated, and polystyrene are used in the treatment of asthma and preterm birth diseases. This study focused on different kinds of nanoparticles like gold, solid lipid nanoparticles (NPs), steroidal and liposome-mediated nanoparticles which are used to treat different pulmonary or respiratory disorders and also examine the current therapeutic techniques for the diagnosis of lung diseases and therapy using nanoscale-based inhalers.

Key Words: *Asthma, Lung Cancer, Nanoparticles, Preterm Birth Disease, Respiratory Disorders, Nano Drug Delivery.*

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Introduction

Nanoparticles (NPs) are very small particles with a diameter of 1 to 100 nm that can be employed in the medical field to diagnose and cure several ailments.[1] Since nanoparticles act as a single unit, they can be used as an effective vehicle for drug delivery.[2] Besides this, nanoparticles can increase the solubility, stability, and bioavailability of the drug with less toxic effects because of targeted delivery.[3] Nanoparticles can be delivered by different routes such as orally, subcutaneously, and by pulmonary inhalation.[4]

Transdermal medication-nanodrug delivery is also under consideration.[5] Liposomes mediated, polymer and dendrimers nanoparticles are some of the most commonly employed nanocarriers in the pharmaceutical industry for dermal or transdermal drug administration.[6] When compared to intravenous treatment, subcutaneous delivery of nanodrugs boosts the efficacy of nanoparticles since the drug remains in the body for a longer period.[7]

The blood-brain barrier and the blood-cerebrospinal fluid barrier control the entry of nano-molecules into the brain.[8] Nanoparticles can break the blood-brain barrier and work at the cellular level due to their small size, therefore their size has an impact on drug delivery.[9,10] For example, liposomes, and solid lipid nanoparticles have been found to successfully transport drugs across the blood-brain barrier. The first medicine delivered to the brain coated with polysorbate 80 nanoparticles was hexapeptide dalargin.[11]

Oral administration is the most common route of medication delivery due to its high level of body acceptance of the patient. The oral route is also the preferred route because of its convenience, efficacy, high patient compliance, and reduced risk of cross-infection.[12] One approach for overcoming the gastrointestinal barrier, protecting the drug from enzymatic breakdown, and releasing it in a

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controlled or systemic manner by nanoparticle encapsulation.[13] The use of biodegradable polymeric NPs is another potential strategy for the pre-oral delivery of protein and peptide medications with improved efficacy.[14]

Compared to alternative delivery methods such as oral or injection, pulmonary delivery has some unique benefits. It avoids hepatic metabolism's initial pass, resulting in lower dosages and fewer side effects. Thus, therapeutics for respiratory illnesses such as chronic obstructive pulmonary disease, asthma, and cystic fibrosis can also be delivered locally via pulmonary track. Other advantages of the pulmonary route include a large surface area with quick absorption due to strong vascularization and avoidance of the first-pass metabolic effect.[15] Nanoparticles may have a longer-lasting release in lung tissue and systemic circulation, resulting in reduced dosage frequency and greater patient compliance.[16] Deposition of nanoparticles in the respiratory tract is determined by diffusional changes generated by the thermal motion of air molecules that interact with particles in the exhaled and inhaled air streams.[17]

Nanoparticle biodistribution and clearance are influenced by their size.[18] Sub-micron sized nanoparticles have advantages over microparticles due to their small size and high mobility. Nanoparticles have a higher cell uptake than microparticles and are available to a broader range of cellular and intracellular targets. Due to their bigger surface area, they have a better loading efficiency than microparticles, which have a far lower loading efficiency.[19,20] For application in the medical field, one must have a thorough understanding of nanoparticle features like form, biological response, size, and metabolism are necessary to make it beneficial in the treatment of disease.[21] Pharmaceutical companies are reformulating conventional drugs by using different types of nanoparticles.[22] Nanoparticles evolved or emerged as a rapidly growing field of research. In this article, we reviewed the nanoparticles applications in respiratory disorders like nanodrug is used as a carrier because it increases concentration and circulation time for the drug delivery at the site of the target area.[23]

Types of Nanoparticles

There are different types of nanoparticles like inorganic, organic and carbon-based. Organic nanoparticles or polymers are generally known as liposomes, dendrimers, ferritin, hydrogels and micelles. These nanoparticles are non-toxic and biodegradable with some having a hollow core, such as micelles and liposomes. Non-carbon nanoparticles are known as inorganic nanoparticles. Inorganic nanoparticles are made up of metal and metal oxide-based nanoparticles. Carbon-based nanoparticles are those that are entirely comprised of carbon. Fullerenes, carbon nanotubes, graphene, carbon black, carbon nanofibers, and activated carbon in nanosize are all examples of carbon nanoparticles.[24]

Gold (Au) is an essential nanomaterial that is used in the electronics and medical field. Gold nanoparticles (Au-NPs) are excellent candidates for transporting biological molecules into cells due to their good carrier capabilities, making them an attractive platform for medication and drug delivery.[25] Nanoparticles enter the body via different routes, including inhalation, ingestion, and diffusion method by the skin. Gold has long been regarded as a noble, inert metal and noncytotoxic having therapeutic and medical properties. Because of its capacity to conjugate with peptides and proteins, gold nanoparticles can be targeted to specific interaction partners.[26] In a chronic obstructive pulmonary disease (COPD) animal model, gold NPs were successfully transported to alveolar epithelial cells.[27]

Solid lipid nanoparticles (SLN) are widely used in pulmonary drug delivery systems and chemically synthesized from phospholipids and triglycerides.[28] Solid lipid nanoparticles have several advantages, including physical stability, preservation of the incorporated drug against degradation, regulated release, and low cytotoxicity. Nanoparticles can also be easily aerosolized into droplets or encapsulated in aerodynamically compatible particulates, allowing for adequate deep lung deposition of an active chemical.[29]

Synthetic polymer-based nanoparticles have a wide range of benefits in various fields. They're easy to create and less likely to harm the environment biologically. Depending on the chemical makeup of its building blocks, each form of the polymer has distinct features.[30] For example polyethylene glycerol coated nanoparticles, (PEG)- can also permeate respiratory mucus due to their muco-inert characteristics.[31]

Nanoparticles in the Treatment of Respiratory Diseases

The respiratory system is an important organ system of the human body that involves the inhalation of oxygen, exhalation of carbon dioxide, and maintenance of the body pH. Respiratory diseases are increasing, with an anticipated 1.8 million deaths. Lung cancer is one of the leading causes of cancer death (18 %).[32] The advanced drug delivery system can offer a new system for the treatment of pulmonary diseases.[33]

1. Lungs Cancer

The lungs consist of the bronchi, blood vessels, lymph tissues, and alveoli. Lungs consist of 500 million alveoli.[34] The alveoli are covered by the layer of phospholipids.[35] The surface tension in the alveoli is reduced by these phospholipids and surface proteins. This reduction in surface tension is necessary for gaseous exchange like carbon dioxide and oxygen.[36] Lungs cancer is the world's second most prevalent cancer. Non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancer cases, while small cell lung cancer (SCLC) accounts for 15% to 20% of all lung cancer cases.[37]

Treatment of Lungs Cancer

Radiotherapy is not advised for the treatment of lungs cancer due to its severe side effects on normal tissues.[38] As an alternative, nano and microparticles can be used to treat lung.[39] Nanoparticles function as a target-sensitive biomarker in the case of lungs cancer.[40] Drugs-based inhalable nanoparticles have also been used to treat lungs cancer.[41] The nanoparticles provide various benefits as a delivery channel for non-invasive medications, particularly for localized treatments, such as lung cancer and the treatment of airway illnesses like asthma, chronic obstructive pulmonary disease, and cystic fibrosis. Anti-cancer medications are regularly administered systemically to treat lung cancer, although this strategy frequently results in sub-optimal therapeutic concentrations of pharmaceuticals at tumor sites and harms the healthy cells and organs. As a result, local inhalation delivery is a viable option for delivering increased local medication concentrations to the specific site. Dry powder inhaler (DPI), a pressurized metered-dose inhaler (pMDI), nebulizer, and soft-mist inhalers are four clinically successful aerosol pulmonary delivery methods.[42] In the case of lungs cancer treatment, nebulizers offer more appealing options for chemotherapeutic drug administration, particularly for drug formulations created as particles of nano-sized in suspensions. Nebulizers are chosen because they can deliver a greater volume of aerosolized medicine in small droplets over a longer length of time.[43]

Nanoparticles in the form of anticancerous drugs proved highly effective in different types of cancers. Nanoparticles decrease the toxic effect of anticancerous drugs in the targeted area.[44] Nanosystems, have been reported to target and administer the medicine in situ to selectively destroy cancer cells, reducing toxicity and adverse effects on healthy organs and tissues. It has been observed that some nanoparticles can overcome tumor resistance. Many types of nanosystems for diagnosis and therapy have been described with promising results, including dendrimer, gold NPs, polymeric micelles, liposomes, and other lipid nanoparticles. Nanoparticles can reach the target region without being identified by the immune system and undergo cellular absorption or deliver the medicine in the tumor proximity due to their biocompatibility and small size.[45]

Anticancerous drugs in the form of nanocrystals are capable of delivering a large number of drugs to the target site. In short, nanoparticle-based drug administration via pulmonary ways can reduce the toxic effects of anticancerous drugs in lungs cancer.[46] Anti-cancer medications' therapeutic index can be improved by enhancing their bioavailability, stability, and residence at specific lung regions using nano-based systems such as liposomes, polymeric nanoparticles, or micelles.[47]

Methods of Nanodrugs Delivery for the treatment of Lungs Cancer

Sedimentation: This method is widely used for the deposition of the particles in the case of nanodrug delivery system.[48] For the treatment of lung disorders such as cystic fibrosis, asthma, respiratory infection, lung cancer, different types of nanoparticles like carbon nanodots and stimulus-response nanoparticles by medical aerosols are used.[49] These aerosols are magnetically targeted.[50]

Nebulizers: This procedure is used for the inhalation of nanodroplets. A nebulizer converts the suspension of nanoparticles into droplet form that can be inhaled easily, therefore, this method is very effective in the treatment of lungs cancer. In routine, nanodroplets are delivered by aerosolization which is another example of nebulization.[51]

Pressurized metered-dose inhalers (pMDI): This procedure is also used to produce droplet suspension of nanodrugs.The aerosols from pMDI cannot be quickly removed from the lungs, therefore, pMDI application in lungs cancer treatment is limited.[52]

Carbon Nanodots: Carbon nanodots are nanoparticles of carbon compounds with specific optical properties due to quantum conformations. Reduction in the size of carbon nanodots results in high compatibility, dispersion, and biochemical reactions. The drugs having amino groups can be attached to C-Nanodots that have carboxylic groups coated on the surface area by an amide linkage. C-Nanodots have replaced toxic quantum dots.[53]

Stimulus–responsive nanoparticles: Stimulus-responsive nano-carrier system shows fast conversion of reversible phase in response to external stimulus and secretes specific contents at the specific site of interest. Pertaining to these advantages,stimulus-responsive core-shell nanocarrier conjugated to folic acid has been developed for lungs cancer treatment (Figure 1).[54]

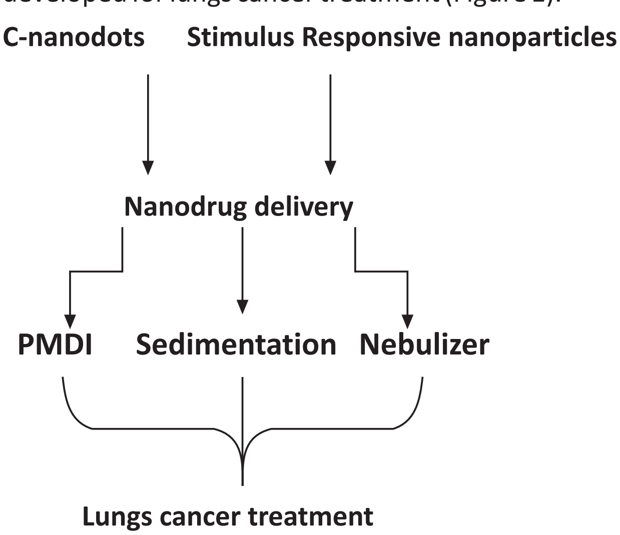

Fig 1: Flow chart representation of nanodrug delivery in lungs cancer treatment

2. Asthma

Asthma is a chronic condition, characterized by inflammation of the airways of the lungs, a persistent cough, wheezing, and shortness of breath.[55] Corticosteroids or bronchodilators are the typical therapies for asthma that can reduce the disease symptoms however their side effects are very prominent. Thus, nanoparticles can be used s to reduce side effects with beneficial impacts in asthma treatment. Gold nanoparticles administered by nasal openings prevent allergen-induced asthma in several murine and reduce the disease symptoms with fewer side effects.[56] These studies show that gold nanoparticles can reduce the asthma symptoms such as airway hyperreactivity, lung remodeling, and inflammation. The protective effects are assumed to be due to a reduction in the production of pro-inflammatory cytokines and chemokines in lung tissue, which is linked to oxidative stress reduction.[57]

Treatment of Asthma

Different types of nanoparticles are used in the treatment of asthma (Figure 2).

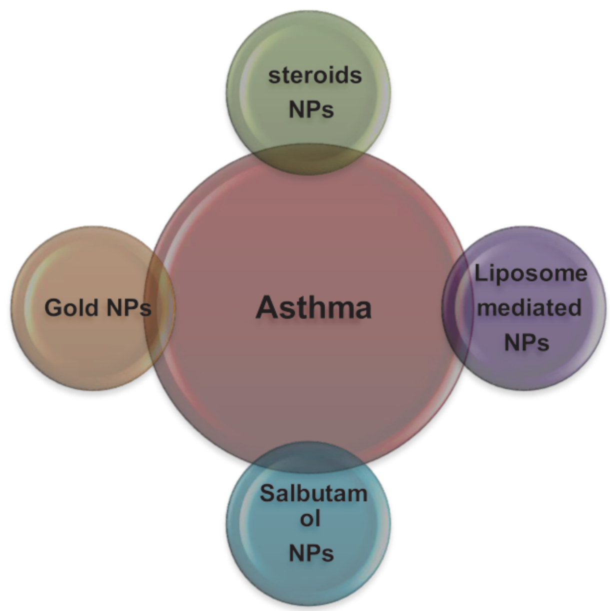

Fig 2: Treatment of Asthma by using different types of nanoparticles (NPs)

Steroidal nanoparticles: Steroidal-nanoparticles are more effective in the treatment of airway inflammation as compared to free steroids.[58]

Salbutamol nanoparticles (SBML): Salbutamol encapsulated in nanoparticles is also used to deliver the drugs to the lungs membrane in case of asthma.[59]

Liposome-mediated nanoparticles: Liposome-mediated nanoparticles of salbutamol sulfate enhance the therapeutic effects by elevating the concentration and retention time of the drug inside the lungs.[60]

3. Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death which is an important chronic inflammatory lung disease.[61] It is due to inhalation of certain particles and gases which leads to inflammation in pulmonary airways that cause dyspnea and obstruction in airflow.[62]

Gold nanoparticles: Au-Nps are used to treat COPD because of their less toxicity. It can be easily coated with any pharmacological compounds.[63]

The gold nanoparticles are administrated to the epithelial surface which is taken up by the alveolar epithelium and gives therapeutic effects to lung parenchymal cells.[64]

Poly (glycerol adipate –co-pentadecalactone) or PGA-co-PDL encapsulated nanoparticles: PGA-co-PDL encapsulated nanoparticles are used for targeted delivery of vaccines and proteins which increase the adsorptive properties of drugs in case of COPD.[65,66] Different types of nanoparticles are used for the treatment of different kinds of respiratory disorders (Figure 3).

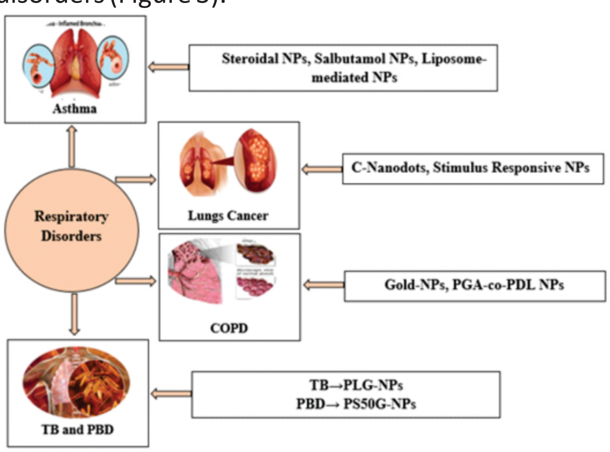

Fig 3: Respiratory disorders- Lungs Cancer, Asthma, Chronic Obstructed Pulmonary Disease (COPD), Tuberculosis (TB) and PBD (Preterm Birth Disease) can be treated by using different types of nanoparticle

4. Tuberculosis (TB)

TB is one of the leading causes of death among infectious diseases.TB has two major categories, pulmonary and extrapulmonary, and is caused by *Mycobacterium tuberculosis* which disturbs the lungs functions.[67,68] TB can be treated by using nanoparticle-encapsulated compounds. Poly DL-lactide-co-glycolide (PLG) nanoparticles associated with anti-tubercular drugs such as rifampicin, isoniazid are used to treat TB.[69]

5. Preterm Birth Disease

Preterm birth is one of the causes of neonatal mortality. Mechanical ventilation leads to preterm birth disease in 20% of infants. Lungs inflammation can be reduced by using nanoparticles subsequently preventing preterm birth.[70]

Polystyrene (PS50G) nanoparticles: Polystyrene nanoparticles are coated with glycine is administered intratracheally to reduce parenchymal lungs inflammation in an adult mouse, PS50g also give same effects in human.[71]

Table 1: Effects of different nanoparticles for the treatment of repiratory diseases by using study models

S. No	Disease	Nanoparticles	Study model	Improvements	References
1	Lungs cancer	C-nanodots Stimulus responsive Nps	Mouse	Effective	53,54
2	Asthma	Steriods, salbutamol Liposome mediated Nps	Mouse	-	58
3	COPD	Gold PDL-co- PGA Nps	Mouse	-	66
4	TB	PGL Nps	Murine mice	-	69
5	PBD	PS50G NPs	Mice	-	71

Conclusion

Nanoparticles offer a wide range of uses in the medical sector due to their small size and vast surface area. We reviewed the use of gold, solid lipid nanoparticles (SLN), steroidal, liposome-mediated, and polystyrene nanoparticles in the treatment of respiratory and pulmonary disorders such as lung cancer, tuberculosis, and chronic obstructed pulmonary disease (COPD), and preterm birth disease. Subcutaneous, oral, and inhalation are administration routes for nanoparticles. In this study, we concluded that nanotechnology is an emerging field to cure different types of respiratory diseases.

Future Perspectives

The beneficial effects of nanoparticles, in the treatment of respiratory disorders, require further research. One aspect could be the evaluation of other biochemical associated-nanoparticles with high impacts and lesser side effects The drug delivery technologies have the potential to revolutionize the drug therapy and catapult it to new heights, but the toxicity of nanosize formulations, on the other hand, should not be underestimated. It is imperative to develop methodologies that can assess both the short-term and long-term toxicity of nanoscale drug delivery devices.

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