"Breaking Barriers in COPD Treatment: The Promise of Nanotechnology-Based Drug Delivery"

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ABSTRACTS:
As the world's population ages and tobacco usage rises, obstructive lung disease is predicted to become a more serious health issue. The only proven preventive measure is quitting smoking. Companies are in a unique position to assist staff members in giving up smoking. Many individuals wait to seek medical assistance until the condition is severe or flares up because lung function continues to deteriorate during the protracted asymptomatic phase. Physicians need to effectively identify and treat this condition in a way that minimizes long-term medical expenses while still maintaining patients' quality of life. The methods used currently for patient care are covered in this article. In the US, Morbidity and death are mostly caused by chronic obstructive pulmonary disease (COPD). The severity of COPD symptoms can vary from moderate to extreme. Patients who are in excruciating pain frequently seek more medical attention, and excruciating pain has a significant role in readmissions due to COPD that last longer than thirty days. One effective strategy to improve bronchiectasis is to utilize two bronchodilators. Furthermore, it has been demonstrated that a number of disease management techniques, such as lung treatment, follow-up visits, follow-up care, respiratory training, and patient education, lower the number of hospitalizations and readmissions among COPD patients.

Key Words: Chronic Obstructive Pulmonary Disease (COPD), Bronchodilators, Polymeric Nanoparticles (PLGA, PEG), Gene Therapy in COPD, Inhalable Nanoparticles, Stimuli-Responsive Nanoparticles

1. INTRODUCTION

The two primary symptoms of this curable and avoidable condition are obstructed airways and COPD stands for chronic obstructive pulmonary disease affects about 16 million individuals in the US. smokers, those with a history of smoking, those over 40, and males are more likely to have the condition. The majority of Medicare patients (up to 71%) do not take maintenance medicine, despite the fact that it is advised for patients with severe COPD. This suggests a potential area for enhancing patient care and management[1]. When lung function is decreasing and symptoms are effectively under control, COPD is deemed "stable." However, "stable" COPD is difficult to treat since it causes frequent or significant harm with diminished lung capacity. worsening of long-term obstructive pulmonary disease, which frequently lead to ER visits and hospital stays, increase the financial expenditures associated with the disease. The severity of the condition is correlated with higher medical costs[2]. The requirement for frequent book reading among individuals suffering from severe obstructive lung disease. This study addresses current management techniques and examines the effects of COPD on people and healthcare systems. In addition to lowering healthcare consumption and associated costs, appropriate healthcare can enhance patient outcomes [3].

1.1. An overview and history of systems NP-based

1.1.1. The history of NP-based drug delivery systems

The application of technology to develop novel therapeutic approaches for lung conditions, such as COPD, is known as nanomedicine. Historically, a wide range of illnesses have been treated with medicinal herbs. But when it comes to medicine distribution, they frequently lack precision, control, and consistency. When Jerkewitz published the first therapy based on polymer-drug conjugate nanoparticles in 1955, he led the way in integrating nanotechnology into medicine to enhance medication delivery and effectiveness. The study of nanocarriers was sparked by the discovery of liposomes in the 1960s. In the 1970s and early 1970s, polymeric and micellar drug delivery technologies were developed 1980s carried on this advancement. 1,005+ Articles about Nanomedicine in 2015. Significant advancements in nanoparticle microengineering, particularly for lung disorders, are made possible by this new discovery, improving the administration of conventional and traditional medications[4,5].

1.1.2. Drug delivery systems based on NP

The majority of COPD medications now in use concentrate on symptom reduction rather than treating the disease that second-hand smoking causes. This emphasizes the necessity of investigating other therapies, such as delivery methods based on nanoparticles (NPs)[6] Therapeutic drugs are encapsulated in nanoparticle-based systems, which then convey them to the target and release the target molecules into the tissue. This technology's dispersion process offers a number of benefits, one of which is the quick delivery of medications for therapeutic uses. Extra carriers that facilitate the transportation and dispersion of active ingredients and therapeutic compounds are frequently included in nanoparticle-based delivery systems. These delivery systems' different distribution modalities also have an impact on pharmacokinetics, convenience of administration, risk of infection, and toxicity. It has been demonstrated that polymeric nanoparticles composed of liposomes, beads, and other materials can cure severe respiratory conditions. In the past, antibiotics, DNA vectors, antibodies, and immunomodulatory compounds have all been delivered to particular targets via nanoparticles. They are well-known for their tissue-specific drug delivery in addition to their capacity to maintain and store medications. When compared to other medicines, this characteristic lessens adverse effects and boosts effectiveness. Furthermore, physical features of nanoparticles, including size, oxidation chemical composition, shape, potential, and zeta potential may be varied to fine-tune cellular responses to them [7]

1.1.3. Pathophysiology of COPD

COPD is characterized by sputum hypersecretion, ciliary dysfunction, respiratory inflammation, structural abnormalities, and physical consequences. Excessive sputum production is a common symptom, but not all COPD patients secrete excessive phlegm. Ciliary dysfunction is caused by squamous metaplasia of epithelial cells, which makes it difficult to remove mucus. Airway cells, specialized in breathing, release of antibodies, and detoxification, play a crucial role in maintaining lung epithelium. Changes in basal cell activity can lead to airway remodelling and inflammation. COPD patients also experience aging, cell growth, senescence markers, and increased lung inflammation due to senescent cells' expression of SASP genes [8]

Telomere shortening and p21 overexpression cause epithelial cells to age faster, leading to increased pro-angiogenic, pro-inflammatory, and matrix remodelling molecules. Bronchitis, an airway condition often coexisting with obstructive pulmonary disease, results in painful episodes and infection. Bronchitis patients have reduced strength, increased airflow blockage, and increased vascular pruning. Chronic bronchitis, smallpox, and emphysema are common symptoms, with emphysema often linked to smoking. To prevent COPD, it is crucial to manage the common cold and avoid AAT deficiency[9]

1.1.4. Traditional COPD therapy

There are several medications available to manage the incurable condition COPD. The severity of the condition should be taken into consideration while choosing a treatment. Risk reduction is the primary management for mild COPD (stage 1), with short-term bronchodilators used as needed. Treatment should involve using one or more bronchodilators on a periodic basis, either alone or in conjunction with corticosteroid medications, as the illness advances (stage II–IV) and lung function deteriorates. In order to treat COPD, doctors advise using bronchodilators, theophylline, anticholinergics, phosphodiesterase 4 inhibitors, biologics, antibiotics, antioxidants, and inhaled corticosteroids in combination. The majority of these therapies include anti-inflammatory and antioxidant medications. They do, however, have a number of drawbacks that might lessen the response, including subpar pharmacokinetics, poor diffusion rate, inconsistent distribution, lower stability, frequent intake, and lack of control[10]

Nanocarriers are thought to be a viable way for improved medication delivery in COPD in order to get around these restrictions. By focusing on certain areas, nanocarriers can increase medication specificity and bioavailability, which lowers dosage needs and boosts patient compliance. Additionally, they have the ability to move dangerous substances via the control system, which lowers toxicity and boosts efficiency. Furthermore, a variety of therapeutic and diagnostic chemicals can be delivered simultaneously because to the diversity of nanocarriers. displeased Systems such as nanocarriers have been created to get around these issues created that increase therapeutic effectiveness by directing medications to the intended location. For instance, one research examined the effects on a mouse model of COPD using betamethasone disodium phosphate (BP) coated in nanoparticles (covert Nano steroids). When applied to the afflicted region of the airways, these nanoparticles serve crucial defensive purposes. A single injection of a 40 μg drug-containing covert Nano steroid decreased BALF eosinophil numbers and kept them there for seven days, while an injection of the same amount of free drug had no discernible impact[4]

An alternate treatment for COPD symptoms is triple inhaler therapy, which combines many medications into a single inhaler. This therapy may help COPD patients achieve better results since it includes ICS, long-acting antihistamines, and a long-acting β2-adrenoceptor agonist. Phase III clinical studies are presently being conducted for novel inhaled medicines for obstructive pulmonary disease, including beclomethasone/formoterol/glycopyrrolate, fluticasone furoate/vilanterol/umeclidinium, and budesonide/formoterol/glycopyrrolate [11]

1.1.5. An overview of COPD

COPD results in bronchial and irreversible lung damage. Breathing problems may arise in the latter stages of the disease. Even commonplace tasks like walking, gardening, and stair climbing might make you gasp during this period. Rather, it expands progressively over time. Constant coughing is one of the symptoms that is frequently mistaken for asthma or a

"normal" smoker's cough. Typically, more severe symptoms are when people recognize they have COPD. The majority of them are now more than 60 years old. Stopping or at least slowing the disease's course is the aim of therapy. Giving up smoking should be your top priority. With this illness, education can be helpful. Medication helps avoid breathlessness and lessen symptoms [12]What your lungs can hold is vast. Your body uses less than a tenth of its lung capacity to store air while it is at rest. This alteration causes lung function to progressively deteriorate with age, yet it has little effect on day-to-day activities. COPD-related shortness of breath only becomes apparent when lung function declines. COPD symptoms include:

- Breathlessness during exercise and, in extreme situations, even when at rest
- A persistent cough throughout the day
- The production of phlegm (a cough).
- Breathing noises, similar to asthma
- Cold and flu symptoms worsen throughout the illness[13]

2. COPD THERAPY OPTIONS USING NANOCARRIERS

Nanotechnology-based drug carriers offer numerous benefits for treating chronic lung disorders, including controlled drug release, anti-inflammatory release, extended application time, reduced side effects, and targeted drug release. These carriers can be used to increase drug solubility, dissolution, and bioavailability. Major types of nanocarriers include liposomes, lipid particles (SLN and NLC), dendrimers, polymer nanoparticles, polymer micelles, liposomes, and nano emulsions. They enhance drug permeability across the nasal alveolar epithelium, making them suitable for COPD treatment. These carriers also aid in drug control, biodegradation, length, and uptake time, lowering dosage, mitigating side effects, and managing the severity of obstructive disease[14]

Because of their multimodal capability, they may be utilized to transport hydrophilic and hydrophobic medications, decrease toxicity, and enhance efficiency all of which can result in the simultaneous application of many diagnostics and therapies in addition to increasing bioavailability and compliance. Nevertheless, there are drawbacks to using nanocarriers. Their appropriateness for certain drug delivery applications is determined by their distinct nanoscale characteristics. Nanocarriers can be made to be passive, inert, stimuli-responsive, slow-degrading, and site-specific in order to accomplish therapeutic effects[15]

Enhanced permeability and retention (EPR) effect, wherein nanocarriers concentrate in sick tissues due to vascular injury, is the primary method of passive targeting, which takes use of the physicochemical characteristics and circumstances of target cells or tissues. The primary goal is to enhance therapeutic results by attaching drug carrier complexes to ligands, such as peptides, nucleic acids, antibodies, or other molecules, which attach to certain receptors on target cells or tissues and deliver the medication to the pain location. To ensure that a medicine is delivered to the illness site effectively and improves treatment quality while minimizing side effects, it is critical to understand the distinction between primary targeting and negative activity as shown in fig.1[16]

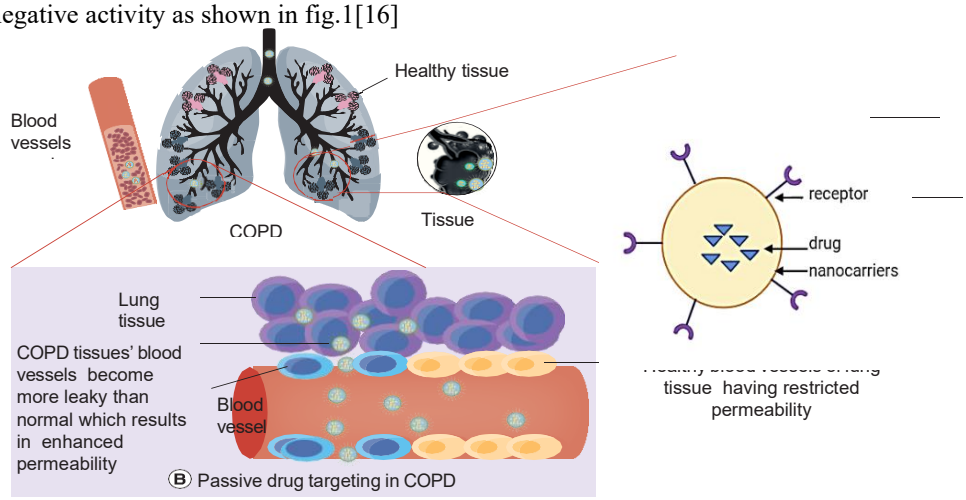


Fig 1. COPD: medication targeting with nanocarriers. The active targets of COPD are represented by (A) and (B), respectively [17].

2.1. Importances of Nanoparticle based drug delivery system

More and more nanoparticles are being employed in the creation of novel nanomedicines that will transcend the constraints of traditional medicine. Clinical and scientific research on the use of nanoparticle-based therapeutics to respiratory issues is reviewed in-depth and up to date in this article. The fundamental makeup and characteristics of nanomaterials have demonstrated their efficacy in the treatment of several ailments [12]. Numerous animal models of lung conditions, such as COPD, cancer, pneumonia, and pulmonary fibrosis (PF) are used to examine the advantages of various nanomedicines and show how they can improve respiratory function. work. therapy for illnesses of the respiratory system. Because these nanomaterials increase the effectiveness of medications and lessen their negative effects, they may pave the way for novel therapies for a range of respiratory disorders. Emphysema, which is characterized by airflow restriction and causes long-term respiratory issues as well as being a major cause of death globally, is linked COPD[14]. The emergence of chronic

inflammation and the overproduction of free radicals are two key elements in the development of COPD. Present therapies include corticosteroids, antioxidants, and antibiotics, frequently call for large dosages and have the potential to have detrimental side effects that render them useless. Drugs conjugated with nanomaterials show promise in treating a range of respiratory conditions since they can be delivered to the microenvironment and are only needed in tiny particles, which lowers treatment costs overall and minimizes adverse effects. Nanoparticles (NPs) of polylactic-glycolic acid (PLGA) are extremely safe since the human body breaks them down fast. As anti-inflammatory, anti-inflammatory, and anti-inflammatory agents, drug delivery into PLGA nanoparticles shows promise[17]. Drug activity, drug carrying capacity, and mechanical characteristics of PLGA NPs can all be enhanced by surface modification. The pathophysiological causes of COPD are briefly reviewed in this paper, along with the function, possibilities, and state of drug-loaded PLGA NPs as a COPD therapy [18].

3. NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS FOR COPD

COPD therapies primarily focus on symptom relief, neglecting side effects, particularly second-hand smoking. This calls for exploring nanoparticle-based drug delivery methods, which encapsulate therapeutic drugs and allow instantaneous control of medication release. These systems impact pharmacokinetics, ease of administration, toxicity, and infection risk. Nanoparticles have shown potential in managing severe respiratory disorders, delivering antibiotics, DNA vectors, antibodies, and anti-inflammatory medications. Their ability to transport drugs with less adverse effects and maintain drugs has made them popular and the timeline graph illustrates a significant juncture in the development of NP-based medication delivery as shown in fig.2 *[19]*

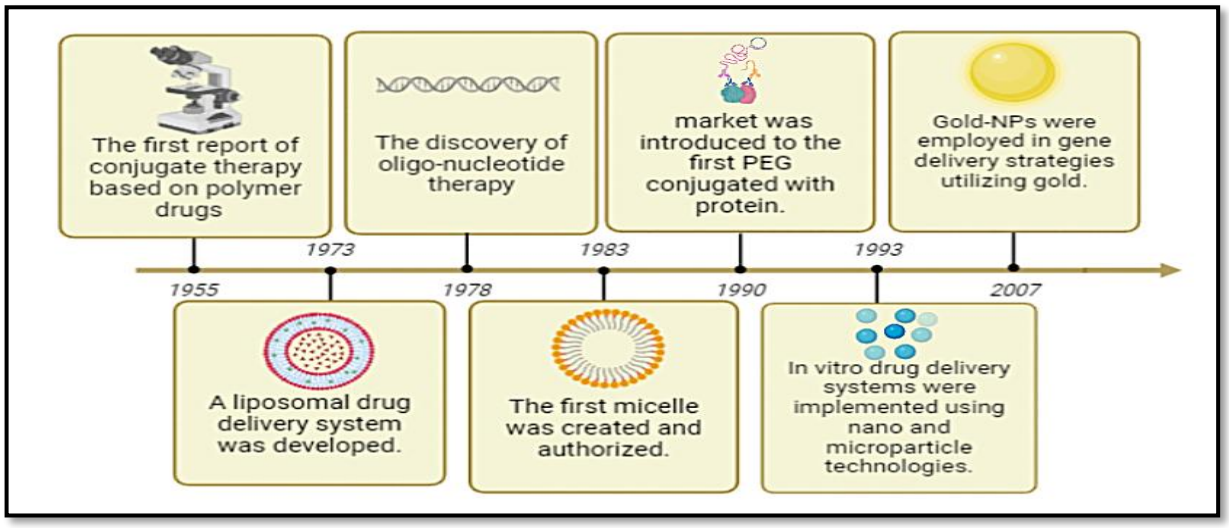


Fig 2. A timeline graph illustrates a significant juncture in the development of NP-based medication delivery.

Effective and able to enter the lower lungs, nanoparticles increase the absorption and bioavailability of drugs. Because of their simplicity, biodegradability, non-toxicity, and biocompatibility, they are a natural therapy technique. Research conducted in vitro by Muhammad and associates. Oil-in-water emulsion solvent evaporation technique (DOTAP) was used to attach miRNA146 adsorbed on polyglyceryl adipate-pentadecanolactone (PGA-co-PDL) nanoparticles to cationic lipid dioleyl groups. According to the study's findings, at the expression of the gene encoding interleukin 1 receptor-associated kinase 1 (IRAK1) decreased by 40% at 0.625 mg/mL A protein involved in stimulating gene expression is encoded by the IRAK1 gene. Furthermore, by suppressing the time gene, the scientists discovered that the miR-146a molecule down-regulated the green fluorescent protein (GFP) the IL-8 promoter of the gene through the IL-1β signalling pathway. Empirical studies indicate that a mix of miRNAs can impact proteins linked to COPD and control the inflammatory cascade accompanying the disease as shown in fig 3[20]

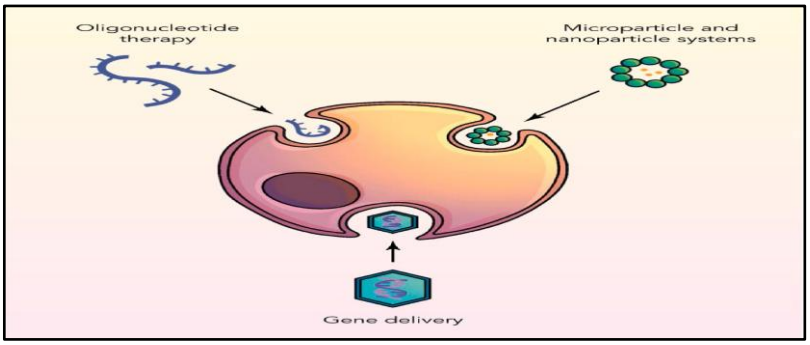
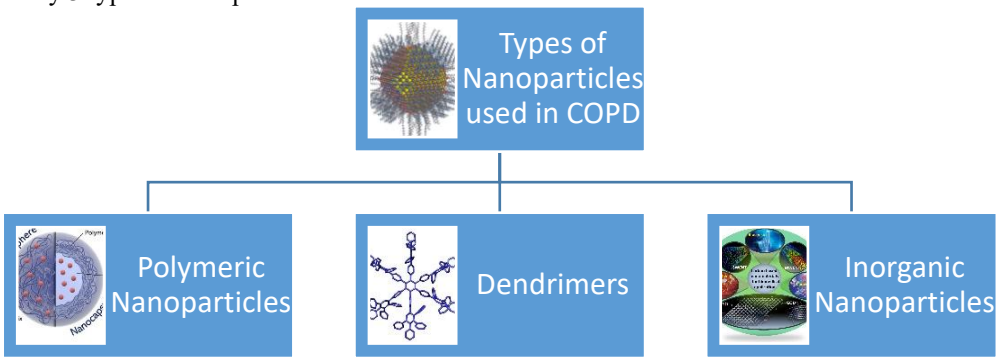


Fig 3. the precise administration of several medications in an effort to cure COPD.

3.1. Types of nanoparticles used in COPD treatment

There are generally 3 types of nanoparticles are used of treatment of COPD are as follows:



3.1.1. Polymeric Nanoparticles

Biodegradable polymers composed of lactic and glycolic acid units connected by ester linkages are known as polylactic-glycolic acid (PLGA) nanoparticles (NPs). After metabolism, PLGA breaks down into carbon dioxide and water, neither of which is harmful to living organisms. Because they are typically smaller than 100 nm, targets and mucosal barriers can be penetrated by nanoparticles without the body recognizing them. This may be seen in the fig.4. The effectiveness of penetration surpasses that of bulk and spherical nanoparticles. Consequently, potent drug release may be impacted by modifying the geometry of PLGA NPs. One major benefit of PLGA nanoparticles over natural polymers is their capacity to encapsulate therapeutic ingredients and shield them from degradation. Encapsulation helps with targeted release by facilitating the active drug's passage across cell membranes[21]

Targeting neutrophils using polylactic-glycolic acid-polyethylene glycol nanoparticles (PLGA-PEG-NPs) in conjunction with ibuprofen was the focus of a recent clinical trial since inflammation is linked to chronic obstructive pulmonary disease (COPD). Chronic obstructive pulmonary disease: inflammation caused by cells Vij (2016) evaluated the physical characteristics of PLGA nanoparticles using a range of methods, including immunoblotting, transmission electron microscopy, quantitative protein analysis, dynamic laser scattering, and release kinetics investigations.[22]Rat models of obstructive pulmonary disease were given PLGA-PEG-NPs loaded with ibuprofen. Upon first assessment, the model's smoke-induced inflammation was shown to have decreased. It was demonstrated that the delivery method is safe and effective, and more investigation is necessary. Enhancing the structure of PLGA-drug conjugates is crucial since they have been shown to be both harmless and efficacious. an overview of the benefits and drawbacks of nanoparticles made of polymers. [23,24]

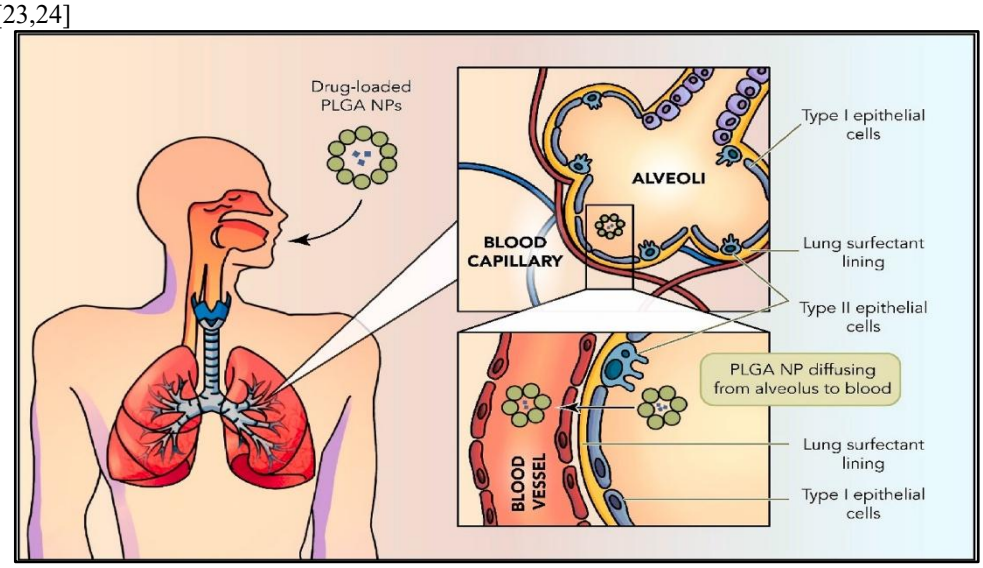


Fig 4. PLGA-loaded NP that penetrates the lung's mucosal barrier. [21,22]

3.1.2. Dendrimers

Synthetic macromolecules known as dendrimers typically have a size range of 10 to 100 nm. Their branching polymeric structures set them apart. Their versatility comes from having a core, an inner repetition layer, and peripheral functional groups. Dendrimers produce spherical forms with highly changeable surfaces during the drug synthesis polymerization process, which contributes to their biocompatibility and ease of degradation. Dendrimers have been utilized in studies to treat lung conditions including asthma and obstructive pulmonary disease. [25] The scientists added lipid modification to the polyamidoamine (PAMAM) and polypropyleneimine (PPI) dendrimers after encasing siRNA within them. It was discovered that this mixture worked in concert to make the dendrimers unique to lung endothelial cells. More importantly, it was discovered that polystyrene (PPE) dendrimers with C15 and C14 cholesterol chains and PAMAM dendrimers with

a C15 cholesterol tail were highly efficient.[26]Dendrimer-lipid complexes did not increase pro-inflammatory cytokine levels, and the mouse model's toxicity-induced weight loss did not materialize, per in vivo data. The antioxidant properties of gold-PAMAM dendrimer nanocomposites were demonstrated to be superior to those of ascorbic acid and gold-core polypropylene mine (PPI) dendrimers. Gold-PAMAM dendrimers' 85-fold higher values than ascorbic acid indicated their potential as powerful agents against oxidative stress. [27]

3.1.3 Inorganic nanoparticles

The morphological characteristics of inorganic nanoparticles are well recognized for reducing peripheral interference from the application site to the target. For instance, magnetic nanoparticles can be directed in either a functional or non-functional way, depending on the characteristics of the ligands that attach to them. An external magnetic field directs them to their locations. The biodegradability of these nanoparticles is contingent upon the metal core's structure. Cobalt, gold, iron, and nickel are found in the metal cores, and the coating is made to have as little contact as possible with the surrounding material. Since the kidneys eliminate non-biodegradable magnetic nanoparticles primarily, possible toxicity and adverse consequences are a cause for worry. According to studies, these nanoparticles have the ability to cross the alveolar capillary barrier, enter blood vessels, and build up in many human organs, including the heart. Numerous consequences may result from this, such as mitochondrial damage, DNA damage, oxidative stress from reactive oxygen species, mechanical impacts, iron toxicity, and damage to the heart membrane and mitochondria. The possible adverse consequences emphasize the necessity of more study and constant observation to guarantee the security of nanoparticles.

Table 1. Advantages and Disadvantages of Nanoparticle based drug delivery system [27,28]

Advantages	Disadvantages
•Compatibility with biological systems. • Extremely steady. •Extremely specialized delivery method. • Needed in little amounts. • Increased surface to volume ratio. • The ability to modify physiochemical characteristics. • Metal nanoparticles have been authorised by the European Medicines Agency and the FDA based on clinical research demonstrating their safety and efficacy. • Advantageous for theranostic and imaging applications.	•Because miRNA is unstable, PLGA-miRNA has not advanced as far in COPD clinical applications. Pharmacokinetic research is necessary. • Possess little therapeutic efficacy. • Possibility of toxicity. •Issues with removal in metallic nanoparticles that are not biodegradable. • Restriction on solubility.

4. TARGETED APPROACHES IN NANOPARTICLE-BASED DDS FOR COPD

There are generally 5 targeted approaches in nanoparticle-based drug delivery system for COPD are as follows.

4.1. Passive Targeting

In order to obtain selective accumulation in diseased tissues without the need for particular formulations, passive targeting in nanoparticle drug delivery systems (DDS) in order to treat COPD, or chronic obstructive pulmonary disease takes advantage of the intrinsic features of nanoparticles. This method reduces side effects and improves performance by taking use of the physiological and pathological characteristics of the lung. This impact is more significant when lung illness is persistent because the lungs' vasculature changes. The EPR effect explains the build-up of nanoparticles in inflammatory and artery-damaged tissues, as seen in conditions like chronic obstructive pulmonary disease (COPD)[29]. In contrast to healthy tissue, sick regions have abnormal vasculature and increased permeability, which make it easier for nanoparticles to penetrate these locations. It alters the pulmonary vasculature, resulting in disruption of endothelial cells and increased vascular permeability. These modifications provide a microenvironment that is favourable for nanoparticle accumulation. Nanoparticles can be preferentially targeted to sick tissue by taking use of these organisms' characteristics, which enhances medication delivery to the intended target. has a significant function in the lungs? Generally, 10–200 nm diameter nanoparticles work well for this kind of application. They can easily enter the alveolar portion of the lungs due to their size. Furthermore, the characteristics of a nanoparticle's surface, such as its hydrophobicity or charge, can influence how well it interacts with lung tissue and increases its retention in medical facilities [30,31].

4.2. Active Targeting

Antibodies or antibodies that detect certain cell signals are used in targeting approaches. Intercellular adhesion molecule-1 (ICAM-1), for instance, is overexpressed on endothelial cells in inflammatory tissues, and nanoparticles can be conjugated to antibodies that specifically target it. Through this targeting process, endothelial cells are encouraged to attach and absorb nanoparticles, which helps transport antibodies straight to the region of inflammation. The capacity of peptides to attach to certain target receptors can be used in their creation or selection. In chronic obstructive pulmonary disease, for instance, integrins which are increased on inflammatory and epithelial cells have a strong affinity for the RGD peptide (arginine-glycine-aspartate)[32].

Researchers can increase therapeutic effectiveness and selectivity for these cells by adding RGD peptides to the surface of nanoparticles. This will increase drug uptake. ligand-targeting. These compounds may be engineered to bind to certain proteins or receptors implicated in the pathophysiology of COPD. For instance, active macrophages in the lungs overexpress folate receptors. Folic acid and nanoparticles can be used to target macrophages and deliver gene therapy or antibodies straight to the infection-causing cells. Short, single-stranded DNA or RNA molecules known as aptamers fold into particular triangles and bind to certain targets extremely well. Aptamers can be engineered to identify and attach to certain bacterial cells found in COPD patient's lungs [33].

4.3. Stimuli Responsive Targeting

The use of pH-sensitive nanoparticles is one of the primary tactics to enhance targeting. Compared to healthy tissues, COPD-affected tissues and organs frequently have a slightly acidic environment. The body's metabolism and components found inside cells create acid, which adds to the acidity of the substance. Although nanoparticles are stable at pH neutrality, their features might be exploited by putting chemical payloads in acidic environments. For instance, polymers coated on nanoparticles might break down or alter in reaction to an acidic pH, releasing the medicine that has been encapsulated right at the site of inflammation. Another innovative method is the use of nanoparticles. Because of metabolic activity and inflammatory reactions, tissue inflammation in regions of hyperthermia in COPD patients may ensue. When exposed to a certain temperature, temperature-sensitive polymer nanoparticles can release their cargo [34,35].

4.4. Combination Therapy

Combination therapy, which uses single-use nanoparticle systems to administer numerous therapeutic drugs simultaneously, is an alternative for COPD therapy (chronic obstructive pulmonary disease). By concurrently addressing many processes, this method seeks to address numerous elements of COPD, including as tissue repair, oxidative stress, and chronic inflammation. Nanoparticles as carriers improve the targeted distribution, stability, and bioavailability of pharmaceuticals, increasing the efficacy of treatment. Take care to account for all aspects of the illness. For example, reducing oxidative stress and inflammation simultaneously can be achieved by combining antioxidants with anti-inflammatory drugs. In the case of COPD, this is especially important because oxidative stress plays a major role in the illness's onset, aggravating the condition and further damaging the lungs. Assemble a multipurpose platform. It is possible to combine hydrophilic and hydrophobic drugs into a single polymer nanoparticle by using materials such as polylactic glycolic acid (PLGA) or polyethylene glycol (PEG). Through the delivery of both drugs to the designated application site, this dual encapsulation optimizes their therapeutic effects.[36].

4.5. Gene Therapy

Gene therapy is the most efficient way to address the underlying genetic and molecular causes of COPD. The delivery of gene therapy through nanoparticles is one way to increase the accuracy and efficacy of therapeutic treatments. The ability of nanoparticles to transport plasmid DNA, microRNA, and small interfering RNA (siRNA and miRNA) across cellular barriers may make them useful for monitoring and the unambiguous detection of lung diseases. Tissue repair is a feature of chronic obstructive pulmonary disease (COPD), which is associated with oxidative stress, chronic inflammation, and a genetic imbalance. Such genetic roots are frequently ignored by traditional medication therapy. Gene therapy aims to alter the expression of specific genes in order to slow down the degenerative process of COPD. Because of their small size, ability to interact with specific ligands, and biocompatibility, nanoparticles provide an ideal platform for genetic product delivery. The goal is pain reduction. TNF-α (tumour necrosis factor-α) and interleukin-8 (IL-8) are two examples of cytokines that can be modified by siRNA to specifically silence their genes. Nanoparticles can encapsulate siRNAs and deliver them directly to the lungs. Moreover, lowering inflammation through cytokine production can improve lung function and decrease disease [37,38].

5. NOVEL FORMULATIONS IN NANOPARTICLE-BASED DDS FOR COPD

In the treatment of chronic obstructive pulmonary disease (COPD), the ability of innovative drug delivery systems (DDS) to target release, maintain release, be biodegradable, reduce dose frequency, and control size and quantity has attracted a lot of attention. These materials address a number of the drawbacks of conventional medication administration methods. The integration of hydrophilic and hydrophobic pharmaceuticals with other biological agents is a particularly good use for nano/microcarriers because of their tiny size, high surface area to volume ratio, and distinctive electrical characteristics. These characteristics provide nano/microcarriers a potentially effective platform for COPD therapy by enhancing the medication's solubility, dispersion, and bioavailability [39]

Examples of novel DDS are shown in the fig.5 and include solid nanoparticles, solid lipid nanoparticles, polymer micelles, dendrimers, nano emulsions, nanosuspensions, microspheres, and microparticles. These carriers can improve patient compliance and the effectiveness of COPD therapy. Their ability to blend in with cell membranes and biocompatibility improve the delivery of medications to the location. Drug control, drug release promotion, prevention of drug degradation, and a decrease in dosage frequency are all achieved by polymeric nanoparticles composed of biocompatible and biodegradable polymers like PLGA. These lipid nanoparticles offer a sustained and regulated release and combine the benefits of polymer and liposome nanoparticles. Increase the bioavailability of hydrophobic medications by solubilizing them. Because of their branch-like architecture, dendrimers may target specific cells or tissues and can load and release drugs in a regulated manner. Drugs that are poorly soluble can become more soluble with the use of nano emulsions and

nanosuspensions, which will enhance their absorption and bioavailability. Biocompatible polymers are typically used to create microspheres and microparticles, which offer regulated release over an extended length of time [40].

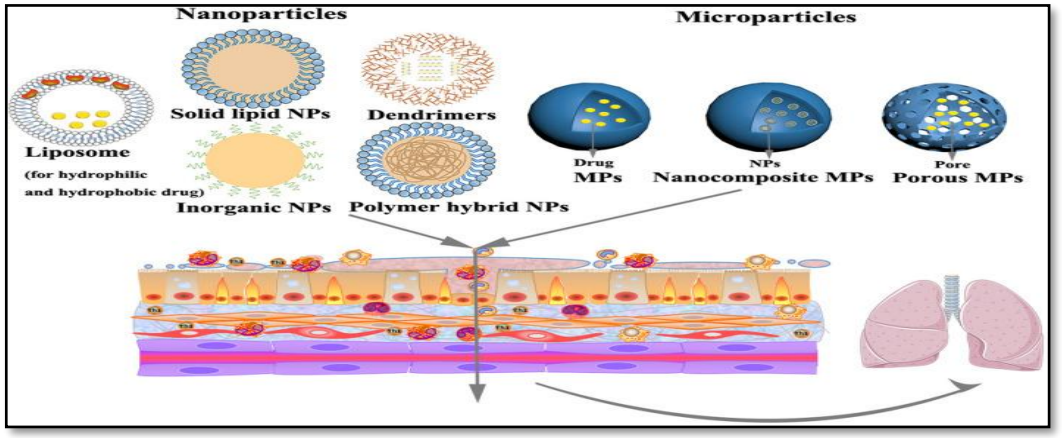


Fig 5. Typical nanoparticles and microparticles that are utilized in COPD to provide antioxidants[39]

6. OVERCOMING CHALLENGES IN NANOPARTICLE-BASED DDS FOR COPD

The use of nanoparticle-based drug delivery systems (DDS) in the treatment of chronic obstructive pulmonary disease (COPD) is recommended due to its capacity to improve drug

Fig 6. Challenges in Nanoparticle-based DDS for COPD

delivery targeting, enhance bioavailability, and decrease adverse effects. But a few issues need to be resolved before it can reach its full potential. These difficulties include making sure the medicine is safe and compatible, making sure the drug loads and releases efficiently, resolving lung biology issues, and managing production and administration. There are 6 Overcoming Challenges in Nanoparticle-based DDS for COPD are as shown in fig 6[40]

Table 2. Challenges in Nanoparticle-based DDS for COPD

Sr.No.	Challenges	Description	References
1]	Ensuring Biocompatibility and Safety	Making sure that the nanoparticle-based DDS for COPD is safe and biocompatible is one of the biggest concerns. To prevent negative consequences, nanoparticles need to be non-toxic, non-immunogenic, and biodegradable. Using biocompatible materials that the body can accept, such chitosan, lipid-based nanoparticles, and poly(lactic-co-glycolic) acid, is one way to get around this problem. Additionally, surface alterations like polyethylene glycol (PEG) coating might improve biocompatibility and lessen immunological recognition.	[41]
2]	Achieving Efficient Drug loading and release	Achieving a regulated release profile and high drug activity is crucial for the therapeutic use of DDS based on nanoparticles. To enhance drug encapsulation, a number of design strategies, including solvent evaporation, nanoprecipitation, and emulsification, have been developed. Furthermore, the synthesis of active nanoparticles can aid in regulating the release in response to particular impacts like pH, temperature, or enzyme activity. For instance, in the acidic environment of sick tissue, pH-sensitive nanoparticles can release their payload and initiate the healing route.	[42]
3]	Navigating Biological Barrier	Numerous biological processes in the lung, such as lymph nodes, alveolar macrophages, and tight junctions between epithelial cells, may prevent the distribution of nanoparticles. To get around these problems, it is possible to create acid-inert nanoparticles that will pierce mucus and evade alveolar macrophage removal. Drug delivery to the brain by nanoparticles may be facilitated by surface modification such as PEGylation or the use of targeting ligands (peptides, antibodies, etc.) that help the particles pass through epithelial cells.	[43]
4]	Improving Targeting and Retention	Enhancing the lung's ability to target and retain nanoparticles is crucial for a successful COPD treatment plan. The primary goal is to functionalize nanoparticles with ligands that bind selectively to receptors like folate receptors or integrins that are overexpressed on bacteria. In order to gather nanoparticles at illness areas, passive targeting takes use of the increased permeability and retention (EPR) effect in inflammatory tissue. Combining two approaches can increase medication delivery's efficiency and specificity.	[44]
5]	Ensuring Long term Stability	The practical application of nanoparticle formulations in the treatment of COPD depends on their long-term safety. Drug delivery, sustained structural integrity, and gradual property release are all requirements for nanoparticles. Using stabilizers that stop nanoparticle aggregation and disintegration as well as improving storage techniques like freeze-drying (lyophilization) are two ways to boost stability.	[45]
6]	Addressing Patient compliance and acceptance	Lastly, patient compliance and acceptance are critical factors in the efficacy of DDS based on nanoparticles. When a delivery is simple, seamless, and enjoyable for the patient, patient compliance may increase. For example, inhalable nanoparticle compositions offer a safe and effective method of medication delivery to patients with COPD. Educating physicians and patients on the benefits and safety of nanoparticle treatment can help boost its acceptance and acceptability.	[46]

7. RECENT ADVANCES AND FUTURE PERSPECTIVES

Recent advances in the causes and treatment of chronic obstructive pulmonary disease (COPD) have opened up new avenues for improving patient outcomes and quality of life. Among these advancements are novel drug delivery systems (NDS), biomarker identification, non-pharmacological applications, and advances in drug therapy. This section discusses some of the most important recent developments and possible career paths in COPD care[42]. With the development of new drugs, COPD treatment has improved. The cornerstone of COPD treatment remains long-acting bronchodilators, including long-acting muscarinic antagonists (LAMA) and long-acting beta-agonists (LABA). However, when dual and triple combination inhalers were launched, symptoms have improved and exacerbations have decreased. Inhalers that

combine LABA and LAMA or LABA and ICS, for example, have been shown to be more effective than monotherapy. In addition to improving lung function and reducing exacerbation rates, triple inhalers (LABA/LAMA/ICS) are recommended. Oxygen and respiratory treatment are two interventional approaches used in the management of COPD.[46]

It has been shown that pulmonary rehabilitation programs that include education, behaviour modification, and exercise training improve patients' quality of life, reduce symptoms, and increase their capacity to exercise. Remote monitoring and management of COPD is now feasible thanks to advancements in digital health and telemedicine technologies, which enable timely intervention and customized treatment[47].

With the identification of COPD biomarkers, the potential for early diagnosis, disease surveillance, and self-management is becoming increasingly clear. The potential use of biomarkers, such as fibrinogen, C-reactive protein (CRP), and blood eosinophil count, to forecast treatment outcomes and exacerbations has been investigated. It should be feasible to identify new therapeutic targets and learn more about the molecular mechanisms underlying COPD by applying omics technologies (genomics, proteomics, and metabolomics) [48].

The goal of novel drug delivery systems (DDS) is to improve COPD treatment's efficacy and safety. Nanoparticle-based DDS, including liposomes, polymeric nanoparticles, and dendrimers, provide drug delivery, controlled release, and a decrease in adverse effects. Small molecules and biological materials can be encapsulated by these systems, which improves their solubility, stability, and bioavailability [49]. For instance, inhalable nanoparticles can minimize harm while maximizing local efficacy by delivering medications straight to the lungs. By replacing and mending damaged tissue, stem cell treatment and regenerative medicine can cure COPD. Because of their anti-inflammatory and anti-inflammatory characteristics, mesenchymal stem cells (MSCs) may be used to treat COPD. Early clinical trials and preliminary investigations have shown the safety and promise of MSCs in the treatment of COPD patients; nevertheless, more investigation is required to ascertain[50,51].

How COPD will be managed in customized medicine in the future, where patients will receive care that is specific to their medical, genetic, and molecular needs. Improved treatment results and lower treatment costs can be achieved by identifying patient groups who react better to certain medications through the application of precision medicine and genomic[50]. Telemedicine, wearable technology, and smartphone health applications will make it possible to manage and monitor COPD continuously. With the use of this technology, which offers real-time data on symptoms, physical activity, and lung function, exacerbations may be identified early and treated promptly [52,53].

8. EMERGING TECHNOLOGIES IN NANOPARTICLE-BASED DDS FOR COPD.

Treatment for chronic obstructive pulmonary disease (COPD) is undergoing a revolution because to the development of drug delivery systems (DDS) based on nanoparticles. This cutting-edge method lessens adverse effects, enhances therapeutic results, and improves medication distribution by using the special qualities of nanoparticles. Below is a detailed examination of some of the most fascinating recent developments in this field[54]

Table 3. Emerging technologies in nanoparticle-based DDS with their recent advancement for treatment of COPD.

Sr. No.	Emerging Technologies	Recent Advancements	References
1]	Targeted Nanoparticles	By selectively delivering medications to the lungs, targeted nanoparticles can increase the effectiveness and safety of treating COPD. The major objective is to bind ligands such as peptides, antibodies, or small molecules to the surface of nanoparticles that bind to bacterially overexpressed receptors. Integrin-targeted nanoparticles, for instance, have been demonstrated to enhance medication transport to lung tissue and offer more therapeutic advantages in a COPD model. enhanced retention and permeability (EPR) and its effects. Nanoparticles made to capitalize on these advantages can target disease sites, lessen damage, and deliver drugs to areas of need more effectively. This technique is quite good at pinpointing the location of lung pain.	[55]
2]	Stimuli-Responsive Nanoparticle	The purpose of stimulus-responsive nanoparticles is to release their therapeutic payloads in response to external stimuli in tissues that are sick. To precisely transport medication to the region of disease activity, for instance, pH-sensitive nanoparticles are made to release medications in the acidic environment of lung tissue. Because of this feature, the drug has fewer negative effects on the body and complements other drugs used to treat COPD (ROS). Drugs produced by nanoparticles can target inflammation and	[56]

		oxidative stress, two important aspects of the pathogenesis of COPD, when there are high amounts of ROS.	
3]	Biodegradable Nanoparticles	The use of biodegradable nanoparticles, such as those made from polylactic-glycolic acid (PLGA), in the treatment of obstructive lung disease, or COPD, has various advantages. PLGA nanoparticles are ideal for drug administration and release since they decompose into innocuous components and are biocompatible. These nanoparticles are increasingly being researched for the delivery of bronchodilators and anti-inflammatory drugs in order to ensure long-term efficacy. Another type of biodegradable carrier that shows promise is the structured lipid carrier (NLC). They offer a versatile approach to drug administration since they can encapsulate both hydrophilic and hydrophobic medications. These lipid-based bacteria have been shown to have the ability to deliver corticosteroids and other anti-inflammatory drugs straight to the lungs.	[57]
4]	Multifunctional Nanoparticles	Due to theranostic nanoparticles' dual therapeutic and diagnostic properties, illness monitoring and therapy can be done concurrently. In cases of obstructive lung illness, these nanoparticles can rapidly prescribe treatment by analyzing lung tissue and administering medication. This dual effect could aid in illness prevention and self-healing.	[58]
5]	Inhalable Nanoparticles	Aerosol technology has advanced to the point where airborne nanoparticles can be delivered directly into the lungs. With minimal exposure, these inhaled medications, such inhalers and dry powder inhalers (DPIs), have local effects. Technologies such as spray drying and freeze drying are used to create dry nanoparticle powders that are suitable for inhalation in order to improve the administration and efficacy of COPD treatments.	[58]
6]	Hybrid Nanoparticles	The advantages of lipid and polymeric nanoparticles are combined in polymer-lipid hybrid nanoparticles, which provide enhanced drug loading capacity, stability, and biocompatibility. These hybrid systems are very useful for administering a mix of bronchodilator and anti-inflammatory medications since they may encapsulate a broad variety of therapeutic substances and offer regulated release patterns.	[59]
7]	Nanoparticles Loaded Hydrogels	Hydrogels filled with nanoparticles provide a new way to administer and release drugs for lung diseases in a controlled manner. Nanoparticles that react to specific stimuli, like changes in pH or temperature, can be included into hydrogels. This reaction guarantees the greatest potential outcomes by ensuring that medication is delivered precisely when and where it is needed. Whether inhaled or injected directly into the lungs, these hydrogels offer a flexible platform for treating COPD.	[60,61]

9. PLANT-BASED NANOPARTICLES LOADED WITH BIOACTIVE COMPOUNDS

Using medicinal herbs to treat obstructive pulmonary disease (COPD) offers substantial therapeutic potential. Plant-based compounds known as phytochemicals have attracted a lot of attention due to their diverse structures and extensive use in both mainstream and alternative medicine shown in fig. 7. Numerous medicinal plants have been used historically to treat conditions affecting the respiratory system, including bronchitis, asthma, TB, and obstructive pulmonary disease[62]. Furthermore, a large number of phytochemicals have antibacterial, anti-inflammatory, and antioxidant qualities, which makes them attractive for the treatment of respiratory illnesses. The plants liquorice root (Glycyrrhiza glabra), pomegranate (Punica granatum), water lily (Nelumbo nucifera), and green tea (Camellia sinensis) are significant in the therapy of lung because of their supposed anti-inflammatory and antioxidant qualities. Low bioavailability, poor permeability and solubility, and quick disintegration are the main reasons why phytochemicals are often restricted. However, the distribution of phytochemicals has improved due to recent developments in medication delivery. Therapeutics based on nanotechnology, such as polymeric nanoparticles (NPs), liposome delivery, liquid crystal nanoparticles, micelles, and nano emulsions, can alter the release patterns of Phyto bioactive substances since they are

stable. A great deal of study has been conducted on phytochemical nanoencapsulation. Drubis et al. and Paul et al., for instance, showed how nanotechnology may be used to enhance the delivery of phytochemicals. In an ovalbumin-induced rat asthma model, Liu et al. (2022) examined the protective effects of 18β-glycyrrhetinic acid (18β-GA) in vivo.
It has been demonstrated that 18β-GA enhances lung function and lowers inflammation in mice studies. It works by stopping nuclear factor kappa B (NF-κB) from becoming phosphorylated in the lungs of mice that have ovalbumin-induced asthma. Furthermore, 18β-GA promotes the heme oxygenase-1 (HO-1) and nuclear erythroid 2-related factor 2 (Nrf2) expression. [63]

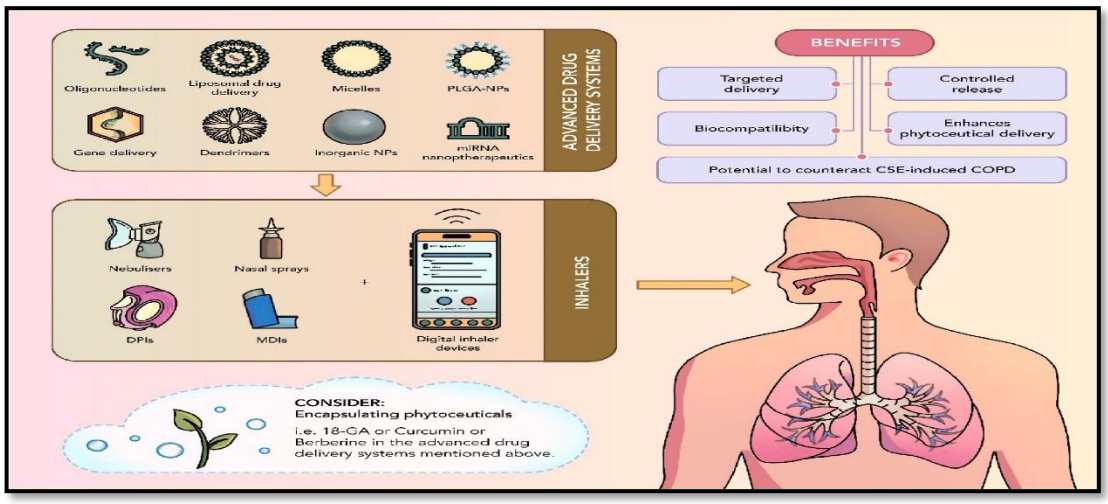


Fig 7. Diagrammatic overview of the roles, uses, and characteristics of several nanoparticle system

According to the researchers, 18β-GA shows promise as a therapy for respiratory conditions including asthma. Its suppression indicates that 18β-GA has to be contained in appropriate nanocarriers. Furthermore, 18β-GA's low bioavailability and restricted water solubility preclude its usage as a routine treatment in clinical settings. On the other hand, adding 18β-GA to the delivery method could increase its bioavailability and enable therapeutic application[64].

10. CLINICAL RESEARCH InNVESTIGATIONS AND PATENTS

The FDA (Food and medication Administration of the United States) is presently reviewing many trials that use medication delivery using nanoparticles (NP) to treat lung cancer and other respiratory illnesses. There isn't much clinical research on COPD (chronic obstructive pulmonary disease), though. However, there is interest in developing nanoparticle delivery via testing before it becomes a medical treatment since respiratory disorders like chronic obstructive pulmonary disease represent a hazard to world health. Although the majority of NP research has been on conditions including cancer, Novel in vivo investigations have exhibited the possible advantages of neural patches in the treatment of chronic obstructive lung disease, asthma, and COPD.
Pegylated immunoconjugates PLGA NPs were utilized by Vij et al. to target neutrophils in obstructive respiratory disorders, such as COPD, to lessen inflammation caused by LPS and to aid in lung tissue regeneration. [73] In a mouse model, their results demonstrated that ibuprofen encapsulation decreased CSE-induced production of inflammatory markers such NFκB and IL-1α ($P < 0.05$), indicating that NP-mediated administration might aid in the regulation of proteases in COPD - Resistance protease imbalance. In a different work, Bohr et al. (2020) looked at the therapeutic applications of miRNA, antisense oligonucleotides, and siRNA to treat chronic lung illness in a mouse model. They transfected siRNA into female Swiss CD-1 mice models of lung illness produced by lipopolysaccharide (LPS) using third-generation PAMAM dendrimers. [65]
TNF-α activity decreased in 4 hours when dendrimers with TNF-α siRNA were compared to those without TNF-α siRNA. But after 72 hours, the dendritic complex activity stops, necessitating more injections. The complex's oxidative and inflammatory characteristics. According to their findings, if phenolic compounds are encapsulated, biocompatible NP complexes may have a longer-lasting therapeutic impact by reducing NF-κB expression and ROS formation. In order to give the optimum therapy, more research and clinical trials are necessary. The potential of NP-based medication delivery for the treatment of chronic obstructive pulmonary disease (COPD) and other significant respiratory disorders is noteworthy.[23]
More than 20 years have passed since the introduction of digital inhalers, commonly referred to as smart inhalers (such as smart pressure metered dosage inhalers). However, they have become more well-known recently, which makes them a crucial component of eHealth for COPD and asthma. The purpose of the tool's development was to gather information on patient adherence for COPD and asthma self-management[66]. Improved lung function, improved breathing patterns, and better symptom management are all correlated with higher inhaler compliance. In order to improve decision-making and patient care, doctors may also use data from the smart water pump to modify medicine use depending on patient behaviours. In spite of these findings, further study and better patient information are required to guarantee customer spending and happiness. Digital inhalers such as Respiro®, Aderium, and Hailie® are examples. [67]

11. FUTURE PROSPECTIVE

When compared to traditional therapy, nanoparticle-based drug delivery systems (NP-based DDS) have enormous potential for the management and treatment of chronic obstructive pulmonary disease (COPD) with enhanced safety and accuracy. These techniques still have issues with toxicity and related adverse effects, despite their numerous positive attributes. The fact that the reduction in size causes the reaction area to rise and subsequently increase in toxicity is a key cause for worry. Further research on the interactions of various nanoparticles under various environmental circumstances is necessary to safeguard patients. Inflammation and harm to genetic material are examples of toxic consequences. The potential for toxicity must be carefully taken into account because the removal of non-biodegradable metal nanoparticles from the body may cause renal failure. Further research is required to assess the long-term risks associated with the use of advanced medications. It's also critical to identify which nanoparticle drugs are appropriate for a given patient, especially for those with varying levels of COPD severity. This change will increase the effectiveness of treatment based on nanoparticles while reducing the risks[68]

CONCLUSION

The treatment of COPD is now possible because to advancements in nanomedicine. In addition to the apparent benefits of improved lung effect targeting accuracy for physicians, incorporating nanotechnology into medication administration may offer further significant advantages. The device's improved control and accuracy over drug administration may result in lower drug intake and higher patient compliance. For individuals with lung conditions, and hence for those with chronic lung conditions, the quality of life has improved. However, more clinical studies are required to validate the results of this advanced technique. Much more study is now needed to properly explore the therapeutic potential of nanoparticles in the treatment of COPD and to ascertain their safety and efficacy in different patient groups. Flare-ups of chronic obstructive pulmonary disease (COPD) can be costly, especially if hospital stays or emergency room visits are required. Frequent exacerbations not only lower a patient's quality of life but also accelerate the illness's course. The frequency of exacerbations has been shown to decrease with adequate use of bronchodilators. However, these treatments are often ineffective, which highlights the need for organizations and physicians to comprehend and follow the treatment plan. According to studies, COPD patients who participate in aftercare programs that improve patient support may experience improved health outcomes and reduced hospital stays. This lesson is complete. It might entail respiratory training, patient education, lung treatment, and a pulmonologist referral. When these steps are combined with appropriate therapy, patients who frequently experience exacerbations may find that their quality of life is improved. Improving COPD care is essential to achieving the greatest outcomes for patients with COPD.

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