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Review article

The application of nanoparticles as advanced drug delivery systems in Attenuating COPD

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a dilapidating condition which is characterized by inflammation, an excess in free radical generation and airway obstruction. Currently, the drugs commercially available for the management of COPD pose several limitations such as systemic adverse effects, including bone density loss and an increased risk of developing pneumonia. Moreover, another limitation includes the need for regular and frequent dosing regimens; which can affect the adherence to the therapy. Furthermore, these current treatments provide symptomatic relief; however, they cannot stop the progression of COPD. Comparatively, nanoparticles (NPs) provide great therapeutic potential to treat COPD due to their high specificity, biocompatibility, and higher bioavailability. Furthermore, the NP-based drug delivery systems involve less frequent dosing requirements and in smaller doses which assist in minimizing side effects. In this review, the benefits and limitations of conventional therapies are explored, while providing an in-depth insight on advanced applications of NP-based systems in the treatment of COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory illness that is distinguished by an obstruction in airflow and inflammation [1]. The inflammatory response component of COPD includes an increase in neutrophil and macrophage concentrations; which contribute to the remodeling of tissues, reduced expiration rates and overall, airway obstruction [2]. All of these attributes contribute to breathing difficulties (dyspnea) in patients suffering from COPD. The World Health Organization has identified that tobacco

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smoking has caused more than 70 % of COPD cases in higher income countries whereas in lower to-middle income countries, tobacco smoking accounts for 30–40 % of COPD cases [3].

Clinical features associated with COPD include chronic airway inflammation, remodeling, and irreparable damage to lung parenchyma, which contribute to the retention of mucous and limits the airflow. This causes dyspnea, irreversible sensitivity of the airways, coughing, wheezing and an increased chest wall diameter. COPD exacerbations often require patient hospitalisations which increases economic burden to the individual and healthcare systems.

The primary risk factor associated with developing COPD is cigarette smoking, as cigarette smoking contains hundreds of pro-inflammatory and pro-oxidant compounds which contributes to the airway inflammation, oxidative stress and irreversible tissue damage. Several *in vivo* and *in vitro* models have been utilized to show how cigarette smoke causes inflammation by dysregulating various signaling pathways within broncho-epithelial cells and macrophages. Thus, generating a pro-inflammatory and pro-oxidant state within the lungs. The release of pro-inflammatory Interleukins [IL-1α, IL-1β, IL8, IL18 and the growth/differentiation factor-15 (GDF-15)] in conjunction with the inhibition of the anti-inflammatory cytokine IL-10, inflammation is typically a result of cigarette smoke penetrating the lung cells [4].

Oxidative stress results from an imbalance between the formulation and elimination of reactive oxygen species (ROS). Glutathione is a cellular mediator which acts as a ROS scavenger. Moreover, tobacco's carcinogenic compounds are conjugated with glutathione as a cellular mechanism of detoxification [4].

COPD primarily affects middle-aged and elderly populations, and its prevalence increases with age. The 2017–2018 National Health Survey identified the prevalence of COPD in populations aged 45 years and older was 4.8 % within the Australian population. This value did not vary greatly between men and women (4.5 % and 5.1 % respectively). Moreover, Aboriginal and Torres Strait Islanders (ATSI) population in 2018–2019 aged 45 years and older had an elevated COPD prevalence of 10 %; comparatively making the ATSI population 2.3x more likely to develop COPD [5].

On an International scale, COPD has been reported to be the third most common cause of death (3.23 million deaths in 2019). Within this reported population, approximately 90 % of COPD related deaths had occurred in populations under 70 years of age and in low-to-middle socioeconomic countries. Overall, COPD has been identified to be the 7th highest cause of poorer health on a global scale [3].

The existing pharmacological therapies for COPD include the use of short-acting beta-2- agonists (SABA) and long acting beta-2-agonists (LABA), long acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS). Typically these medications are selected either as a monotherapy or in combination based on the patient's symptoms and severity of COPD [6]. Whilst these therapies can only provide symptomatic relief, they have substantial side effects [1]. Non-pharmacological management measures for COPD include smoking cessation, physical activity, pulmonary rehabilitation, vaccinations, bronchoscopic lung volume reduction surgery and adequate nutrition [6–8].

The conventional pharmacological treatments, and relative dosage forms employed, pose limitations including their ability to only provide symptomatic treatment, and carry extensive side effects partly due to the systemic exposure to the therapeutic agents subjected to the patients. Therefore, a potential solution that has the potential to have fewer side effects is represented by the use of targeted drug delivery systems, which aim to deliver their therapeutic drug to target tissues to produce the therapeutic effects [9]. NP-based delivery systems have the potential to increase patient outcomes. Generally, nanoparticles have physiochemical properties which make them highly desirable and have demonstrated therapeutic potential to treat various debilitating respiratory morbidities including COPD. Moreover, it has been demonstrated that organic nanoparticles can increase the bioavailability of drugs and are highly selective in their penetration which makes them a suitable drug delivery for various health conditions [10].

In this review, we will explore the various advanced and nanoparticle-based drug delivery systems that are currently being investigated as therapeutic strategies, to highlight their efficacy and potential to treat COPD. To accomplish this, we searched on PUBMED '*nanoparticles as advanced drug delivery systems COPD'* which was filtered to share papers over the last 10 years. From this, 27 matches appeared. Similarly, other keywords including '*COPD'* and '*PLGA'*, where searched and 12 papers were found and analyzed. Other keywords included '*COPD pulmonary delivery limitations'*, '*phytoceuticals*, '*COPD nanotherapeutics*' and '*liposomes'* where also used to generate research.

2. Limitations of current COPD therapies

2.1. Advantages and disadvantages of conventional therapies

The Rodrigo systematic review in 2017 utilized 23 Randomized Control Trials (RCT) to collect data and demonstrate the statistical significance and clinical benefit of combinational LABA with LAMA versus either drug class as a monotherapy for first-line management of moderate-to-severe COPD patients [11]. This can be used as a support to the current approved first-line therapies used in clinical practice for COPD patients. LABAs including formoterol and indacaterol activate beta-2-adrenoreceptors, resulting in the relaxation of smooth bronchial muscle cells [12]. LABAs have a duration of action of approximately 12 h and have been shown to significantly reduce exacerbation frequency and enhance lung volume thus, improving Forced Expiratory Volume (FEV1) measures (the volume of air exhaled during a forced breath in a measured amount of seconds) [13]. However, they have no effect on the rate of declining lung function on the patient mortality. Moreover, these drugs have adverse effects which include somatic tremor, cardiac rhythm disturbance and hypokalemia [12,14]. Comparatively, the Rodrigo 2017 study analysis challenges the presence of such side effects as it notes there is no increase to severe cardiovascular events based on their extrapolated safety data [11]. Other side effects identified

by the Rodrigo 2017 study, associated with the conventional use of dual LABA/ICS therapy, include an increased incidence of pneumonia, which can cause further complications to the patient as shown in Fig. 1.

Comparatively, LAMAs such as tiotropium and umeclidinium are inhaled anticholinergics which inhibit muscarinic M3 receptors in efforts to prevent bronchoconstriction [12]. LAMA treatments provide symptomatic relief which can include a reduction in cough and sputum, as well as reducing severe COPD-induced exacerbations which often require hospitalisation. LAMA have also been shown to increase the effectiveness of programs such as pulmonary rehabilitation. Whilst inhalational administration of anticholinergics have poor absorption compared to the systemic administration, this has found to be beneficial as it restricts severe potential systemic side effects. The main reported side effect of LAMA includes mouth dryness and bitterness in the mouth, especially with the use of ipratropium [14].

As a result of the favorable mechanisms of action of both LABA and LAMA, it is advantageous to co-administer the drug classes in the management plan to maximize bronchodilation for patients with uncontrolled COPD or patients who had an inadequate response to monotherapy [12,14]. The combination of LABA and LAMA has been shown to reduce severe COPD exacerbations [15]. In addition, there are a variety of dosing options available, wherein the delivery can be achieved from a fixed-dose single inhaler containing both LABA and LAMA which will reduce pill burden and increase medication adherence, or by using multiple inhalers designed with specific dosing regimens.

Inhaled Corticosteroids (ICS) can reduce airway hyper-reactivity when being used as anti-inflammatory maintenance therapies for patients with COPD [16]. ICS's are commonly utilized in conjunction with LABA medications to enhance health status and improve lung function in patients with severe COPD exacerbations [17]. According to the RCT studies that were conducted over 6–12 months, the dual therapy comprising of a bronchodilator with an ICS demonstrated an increase in FEV1. However, in trials where the ICS was a monotherapy, the RCT's failed to show a clinically significant effect [16,18,19]. Patients who generally benefit from undergoing ICS treatment include those who have experienced more than 2 COPD exacerbation-induced hospitalizations annually, a blood eosinophil count of >300 cells per microliter and a history of asthma. However, the drug selection for a suitable therapeutic strategy for COPD should be based on the therapeutic goals for the patient. If survival is the primary target, a balance between clinical judgement and a risk-to-benefit analysis is critical in deciding if using an ICS is appropriate for the patient [17]. One of the major limitations of administering ICS use is that they inhibit monocyte chemotaxis, T-cell activation, interleukins (IL), and tumor necrosis factor-α (TNF-α) secretion. This contributes to the increased risk of patients developing pneumonia [15,18]. The risk factors associated with the development of pneumonia in patients utilizing ICS includes age (>55 years), an FEV1 between 30 and 50 % and a history of low eosinophil

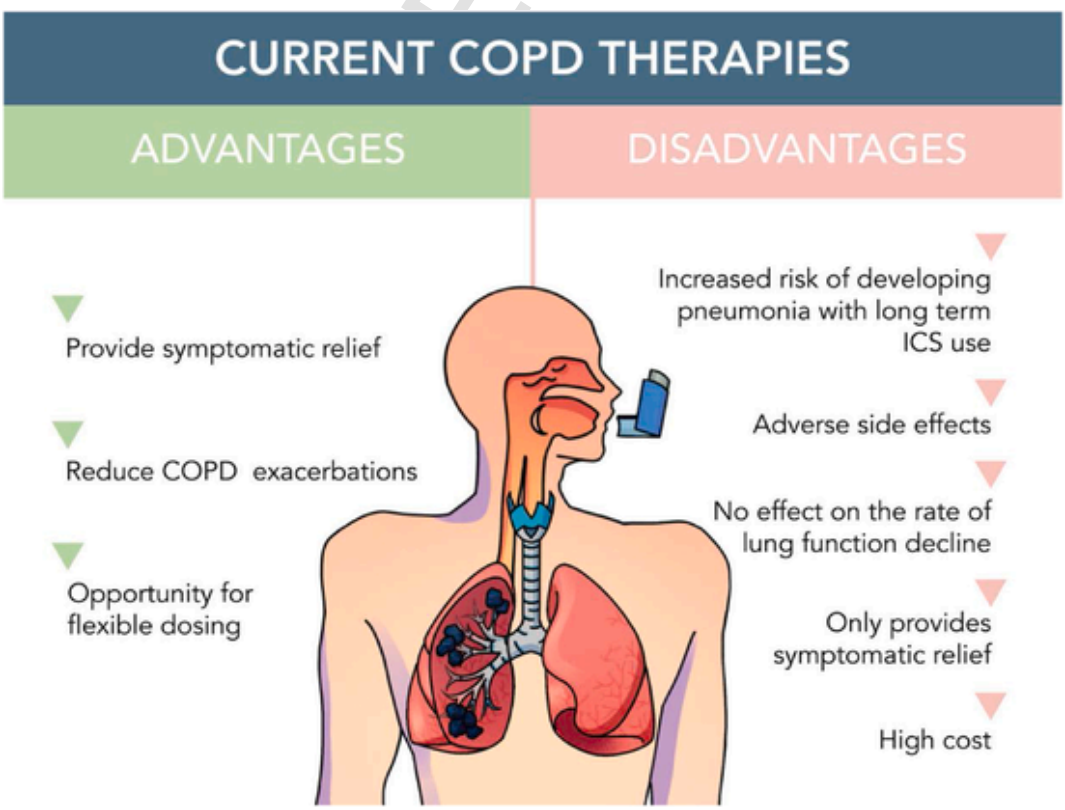

Fig. 1. The advantages and Disadvantages of conventional COPD Therapies. Whilst conventional therapies have benefits including flexible dosing regimes and their ability to reduce COPD exacerbations and hospitalisations, their effectiveness is limited by factors including adverse side effects, and their inability to reverse the patient's decline in lung function.

count [19]. As COPD is a disease commonly targeting an older population demographic, it naturally increases the associated risk of developing pneumonia. This is further confirmed in the Janson observational study which highlighted that there was no statistically significant survival benefit in the dual use of LABA/ICS. Instead, 20 % of patients in the treatment arm endured at least one pneumonia event in comparison to the placebo group (12 %) [20,21].

3. The history and review of NP-based systems

3.1. The history of NP-based drug delivery systems

Nanomedicine is a medicinal application of technology and potentiates an effective delivery of futuristic novel therapeutic strategies for inflammatory lung illnesses including COPD [22]. Historically, medicinal plants were utilized to treat diseases however they lacked consistency, control and specificity in the drug's delivery. The combining of medicine with nanotechnology to advance the delivery and efficacy of medicines was first demonstrated by Jatzkewitz in 1955 where he reported the first polymer-drug conjugate NP-based therapy. Similarly, in the 1960's liposomes were discovered which birthed the research field of nanocarriers and the development of micelle and polymerization drug-loading techniques in the late 1970's – early 1980 (Fig. 2) [23,24]. The number of publications under this field of research has exponentially grown where in 2015, it was reported that *Web of Science* had published more than 1000 nanomedicine research articles detailing information on nanoparticles including nanocarriers in utilized biomedical settings. As a result of this growing research area, the micro-engineering of NPs to advance drug delivery of conventional and traditional medicines and has been applied to many inflammatory lung diseases [24].

3.2. NP-based drug delivery systems

As mentioned previously, the current therapeutic approaches target symptomatic relief but do not specifically treat the cause of the COPD, namely the damage done by cigarette smoke [4]. From this stems the necessity to explore other therapeutic options such as nanoparticle (NP) based delivery systems. NP-based drug delivery systems (shown in Fig. 3) are formulations which encapsulate the therapeutic agent, deliver the agent to the target site then liberate the active molecules into target tissues. The dispersing process of these technologies have many benefits including a controlled release of the available drug in real time to the therapeutic target. The NP-based delivery systems are generally composed of the drug molecules and additional carriers that assist in the diffusion and transport of the active ingredient. Additionally, the various routes of administration of the drug delivery systems will contribute towards other factors including the risk of infection, toxicity, pharmacokinetics and ease of delivery.

Nanomedicine including silver and gold inorganic nanoparticles, nanotubes, micelles, liposomes, polymeric nanoparticles, to name a few have displayed great therapeutic potential as a therapeutically effective treatment option for severe, respiratory diseases. Historically, NPs have delivered antibiotics, DNA vectors, vaccine components and immunomodulatory molecules to their respective target sites. Furthermore, nanoparticles are favoured due to their ability to protect and stabilize the drug, but also because they allow tissue-specific delivery of the drug. Consequently, this reduces side effects to the patient and has enhanced efficacy in comparison to

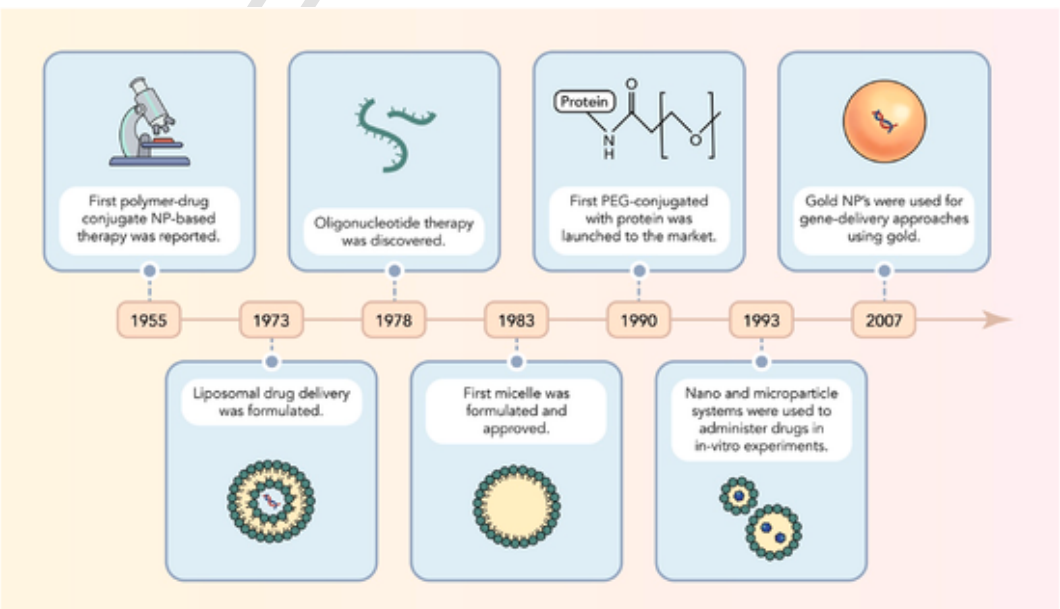

Fig. 2. A graphical timeline identifying historically significant timepoints for NP-based drug delivery systems.

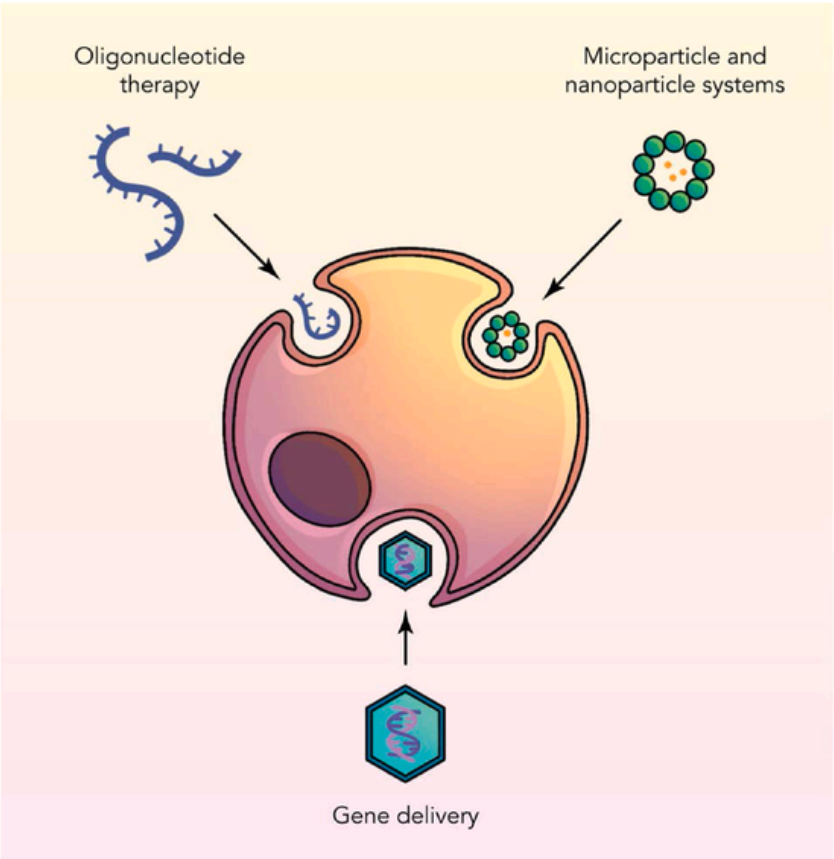

Fig. 3. A visual diagram depicting the various types of drug delivery systems which are being explored to potentially optimize the targeted delivery of various drugs in efforts to treat COPD.

other treatment options. Moreover, the cellular response of nanoparticles can be fine-tuned by adjusting physical characteristics such as size, oxidative potential, zeta potential, composition, shape and chemical composition [1].

De Rubis et al. (2023), conducted a study which utilized a poloxamer 407-based nanoemulsion to deliver agarwood essential oil (Agarwood-NE) to determine its efficacy on an *in-vitro* COPD model obtained by treating human basal epithelial cells treated with 5 % cigarette smoke extract. The study reported that the Agarwood-NE demonstrated anti-inflammatory activity on the cigarette smoke-treated cells by inactivating pro-inflammatory cytokines and mediators including IL-8, GDF-15, IL-1β and IL-1alpha; as well as by activating pathways which produce anti-inflammatory cytokines and their respective mediators including GH, IL-10 and VDBP. Moreover, the study reported that the Agarwood-NE has the potential to counteract cigarette-smoke induced damage to lung tissue via inducing molecular pathways which naturally protect the lung cells from damage and are proactive in mucosal healing. Thus, the nanoemulsion of agarwood oil extract proved to be a potential therapeutic strategy for inflammatory diseases such as COPD [4].

Similarly, Paudel et al. (2022), assessed the protective action of phytantriol-based liquid crystalline NPs encapsulating the phytochemical on cigarette smoke-induced inflammation and oxidative stress on human bronchial epithelial cells. The study highlighted the benefits of adopting a nanotechnological approach to increase the bioavailability of the berberine which resulted in an observed higher potent biological activity during the *in-vitro* study. The study demonstrated that a lower dose of crystalline NP-loaded berberine was required to exert the same therapeutic effect as free berberine where dose was 5-folds higher thus, further supporting the notion that encapsulation into nanoparticle-based drug delivery systems and the adoption of nanomedical strategies improves the delivery of many natural products that have unfavorable physiochemical properties [25].

Furthermore, to overcome the side effects caused by ICS as mentioned *vide supra*, liposomes and nanoparticles have been developed which offer a novel delivery system that can overcome the ICS limitations. Liposomes particles encapsulating glucocorticoids can be designed with precise drug-loading capabilities. When administered via the pulmonary route, these particles can target the lungs directly, enhancing drug efficacy while reducing systemic exposure and associated side effects.

Studies have shown the potential of liposomes and nanoparticles for delivering glucocorticoids to the lungs. For instance, a study by Konduri et al. demonstrated that liposomal encapsulation of budesonide improved their therapeutic efficacy in a murine model, reducing airway inflammation and bronchoconstriction as shown in Table 3. Treatment with weekly therapy of encapsulated budesonide was found as effective as daily budesonide therapy, a major issue with patient compliance, in decreasing lung inflammation by lowering eosinophil peroxidase activity, peripheral blood eosinophils, and total serum IgE levels [26]. In another study by Matsuo et

al. evaluated nanoparticles betamethasone disodium phosphate (BP) encapsulated in biocompatible, biodegradable blended nanoparticles (stealth nanosteroids). These stealth nanosteroids were found to accumulate at the site of airway inflammation and exhibit anti-inflammatory activity in a mice model [27].

In another study by Oh et al., budesonide loaded porous PLGA microparticles and results indicated that numbers of inflammatory cells present in bronchoalveolar lavage (BAL) fluid and also in tissue sections were markedly reduced (Table 3). A significant reduction in bronchial hyperresponsiveness of asthmatic mice was also observed after the treatment with budesonide-loaded porous PLGA microparticles [28].

However, despite significant advantages of NP based drug delivery systems further research is needed to optimize the formulation and understand the long-term safety and efficacy of these delivery systems. Nevertheless, these newer approaches have great potential for the treatment of respiratory diseases and improving patient outcomes.

3.3. Microparticle and nanoparticle systems

Nanoparticle polymers have been adopted due to their highly effective ability to access the lower regions of the lung thus, increasing drug permeability and bioavailability [29]. Moreover, they are a highly desirable therapeutic strategy due to their biocompatibility, low toxicity, flexible physicochemical surface protein modifications and their biodegradability. An in-vitro study by Mohamed et al. utilized miRNA146 adsorbed onto a Poly(glycerol adipate-*co*-pentadecalactone (PGA-*co*-PDL) nanoparticles using an oil-in-water emulsion solvent evaporation technique to combine the NP with the cationic lipid dioleoyltrimethylammoniumpropane (DOTAP). The study demonstrated that there was a dose-dependent effect where a dose of 0.625 mg/mL reduced the Interleukin 1 Receptor Associated Kinase 1 (IRAK1) gene expression by 40 %. IKAK1 is a protein-coding gene which plays a functional role in regulating inflammatory gene expression. Additionally, the study identified that the miR-146a molecule was able to maintain its functional structure during the gene silencing and it also reduced the IL-8 promoter reporter, Green fluorescent reporter (GFP), via IL-1 beta signaling pathway. The study suggested that the designed miRNA could regulate the inflammatory process of COPD and access relevant target proteins [30].

One of the main limitations of commercially available drug delivery approaches include low mucosal penetration, poor patient adherence, poor biodistribution of the active ingredient and the internal organ environment which influences drug absorption. These limitations can be resolved by employing nanoparticle and microparticle drug delivery systems. They can be designed with the ability to prolong the circulation time of the drug in the blood, which will result in a reduced likeliness of toxicity and contribute towards a sustained drug release [31]. The following paragraphs will describe nanoparticle and microparticle delivery systems in greater detail.

3.4. Oligonucleotide therapy

Oligonucleotide therapy aims to modulate the expression of a target gene by preventing translation. The concept of oligonucleotide therapy was originated from Zamecnik and Stephenson in 1978. Research in RNA-targeting approaches in *in-vitro* studies have attempted to determine the therapeutic potentials of siRNA, ribozymes and miRNA. This extensive research has highlighted the major benefits including the highly efficient approach in targeting mRNA and its ability for multiple protein copies to be synthesized. Thus, making oligonucleotide therapies a promising resolution for targeting COPD [32].

Antisense oligonucleotides are single-stranded DNA (or RNA) which have a complementary binding with target mRNA which results in gene knockdown. When antisense oligonucleotides target (ASO) mRNA, they act on RNase H-mediated cleavage of ASO-targeted mRNA; resulting in the degradation of the target mRNA. Importantly, the ASO remains unchanged after this interaction which allows it to be re-used. Comparatively, siRNA target gene silencing mechanisms to reduce a specific sequence of target mRNA. Similarly, miRNA are endogenous molecules which target the regulation of transcriptional and post-transcriptional gene expression thus resulting in responses including apoptosis, inflammation, proliferation and cell differentiation [33,34].

Optimising the structure and concentration of the selected type of oligonucleotide therapy is imperative to enable the therapy to pass physiological barriers and reach the entry site of the targeted cells. It is believed that adsorptive endocytosis and fluid phase pinocytosis are the primary mechanisms of action for oligonucleotide therapy [33].

Oligonucleotide therapies have demonstrated great therapeutic potential to treat human diseases and have recently obtained FDA approval for some human diseases. The Antisense therapy, Kynamro has been FDA approved for the treatment of homozygous familial dyslipidemia as an example [33]. Specifically in treating COPD, there was a Phase I randomized, double blinded, placebo-controlled study which aimed to determine the safety and tolerability of the repeated inhaled doses of the clinical trial drug, TPI 1100 in healthy subjects. However, the study was discontinued before the start-up of the clinical trial [35]. There have been other phase II clinical trials which utilized oligonucleotide therapies to treat asthma however, these trials have also been discontinued [33].

Furthermore, miRNAs based nanotherapeutic systems have also been developed. MiRNAs are naturally highly important due to their ability to identify different functional states and dysregulation of chronic respiratory illnesses. Thus, they are critical in regulating homeostasis as abnormal expressions of miRNA can contribute to diseases such as cancer and viral infections. In cases where upregulation of miRNA has been identified, antagomirs (anti-miRs) have been favorable in delivering promising outcomes. Once considered as silencing agents in 2005, antagomirs are classified as antimiRNA agents (new oligonucleotide group) which act in a specific and complementary mechanism to their respective miRNA targets. However, one limitation to this type of therapeutics is comparatively reduced ability to cross cellular membranes without the aid of a polymer-based drug carrier [45].

As COPD is characterized by excessive inflammation, lesions in the alveoli and airflow limitation, evidence has demonstrated that the upregulation/downregulation of miRNAs contribute to the pathogenesis of COPD. Baker et al. highlighted that inhibiting elevated

miRNA-570-3p induced by oxidative stress within airways using antagomiR can restore the expression of the anti-ageing molecule, sirtuin-1, thus regulating lung aging and immune senescence. In the long term, this will re-establish cellular growth and lower abnormalities affiliated with cellular senescence [46,47].

Moreover, inhaled drug delivery is ideal for oligonucleotide therapy as the respiratory tract is naturally lined with pulmonary surfactants (zwitterionic lipids) which aid in the adsorption of oligonucleotide therapies by target cells [32,33]. Moreover, this mechanism provides direct access to the target site and slower degradation of the complex thus, retaining the therapy within the lungs for prolonged times. This can reduce the dosing frequency thus, reducing systemic toxicity. However, further research is needed to assess the long-term clinical safety of the therapy. Nevertheless, chemical modifications to increase the oligonucleotide efficacy is also desired [32].

3.5. Gene delivery

Gene therapy has also demonstrated promising results in the treatment of lung disease [29]. In a study by Kim et al., acute lung injury (ALI) which is an inflammatory disease, was targeted by loading curcumin into micelles and administered into affected mouse models. The gene delivery efficiency was measured using luciferase assays to identify the effect of co-delivering curcumin and the heme oxygenase-1 (HO-1) gene. Curcumin was loaded with plasmid DNA which underwent a process of charge interactions. The HO-1 plasmid complex (approx. 120 nm in size) was later delivered to the lung tissue cells. The developed compound demonstrated the ability to reduce pro-inflammatory cytokines and reduced hemolysis in edema [36]. Thus, the curcumin-loaded complex (PamChol-Cur) was successful in demonstrating the efficacy of this specific gene delivery in pulmonary diseases.

4. Nanoparticle applications in COPD

4.1. Polymer-based nanoparticles

4.1.1. Polymeric nanoparticles

Poly(lactic-*co*-glycolic) Acid (PLGA) NPs are biodegradable polymers, which consist of lactic acid and glycolic acid, bonded together via ester linkages [37]. When metabolized, its counterparts consist of water and carbon dioxide, which are considered non-toxic to tissues. Typically, nanoparticles are less than 100 nm in size [1], making them optimal for crossing mucosal barriers and immune defense lines when reaching their target site as shown in Fig. 4. Moreover, the smaller sizes of PLGA NPs make them ideal for airways due to an easier diffusion and a reduced steric interference. Typically, elongated spheroids and honey-comb shaped PLGA NPs have higher penetration efficiencies due to their higher surface-to-volume ratio in comparison to other geometries such as spheres. Thus, modifying the PLGA NP shape will influence the release of the active molecule [38]. What makes PLGA-NPs desirable in comparison to natural polymers is their ability to encapsulate the therapeutic agent thus, protecting the agent from depredation. This function enables the active ingredient to pass cellular barriers and have a targeted release [37,39].

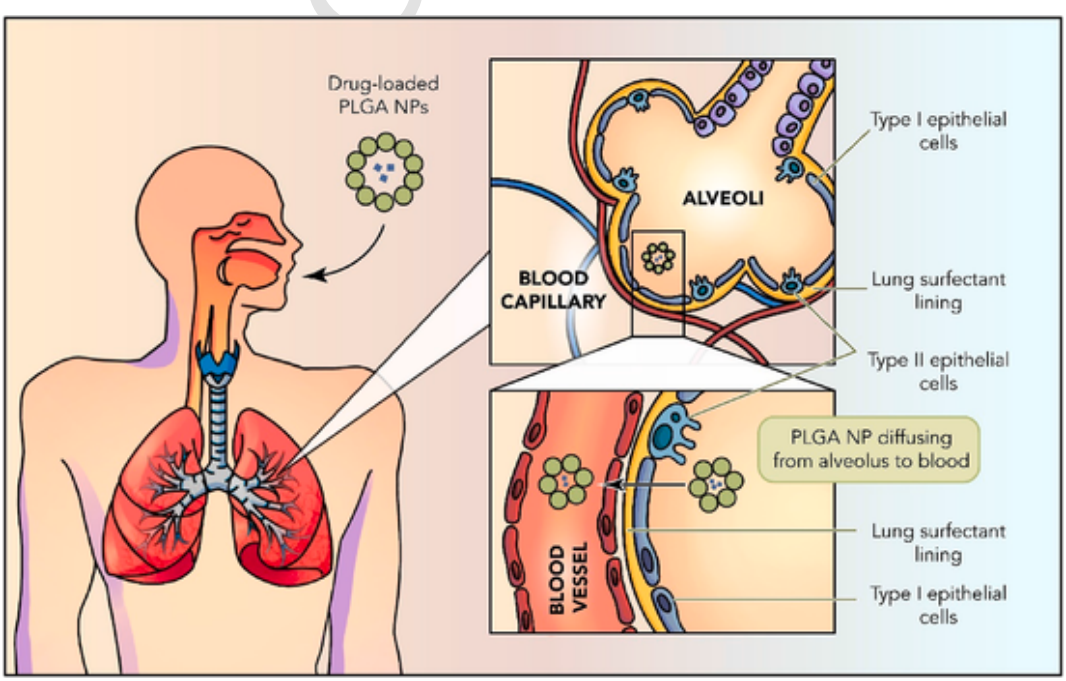

Fig. 4. A visual representation of a PLGA-loaded NP crossing mucosal barrier in the lungs.

As COPD is an inflammatory condition, there have been clinical applications, which utilize ibuprofen as the therapeutic agent with Poly(lactic-*co*-glycolic) Acid-polyethylene glycol-nanoparticles (PLGA-PEG-NP) delivery with the intention to target neutrophil-mediated inflammatory responses in COPD [38]. The Vij (2016) study utilized dynamic laser scattering, transmission electron microscopy, protein quantification assays, immunoblotting and release kinetic studies to characterize the physical properties of the PLGA nanoparticles. The PLGA-PEG-NP was loaded with ibuprofen and delivered into murine models of obstructive lung diseases as shown in Table 3. Overall, the study utilized real-time imaging to determine that the delivery had significant therapeutic efficacy in inhibiting cigarette smoke-induced inflammation in the murine models [39,40].

Whilst PLGA delivery systems have been shown to be effective and safe, limited pre-clinical research has been conducted. Thus, it is of high importance to perform more research in enhancing the formulation of PLGA-drug conjugates due to their elevated level of reported efficacy and low levels of toxicity [39]. A summary to the advantages and disadvantages of polymer-based NP's is displayed in Table 1.

4.1.2. Dendrimers

Dendrimers are synthetic branched polymeric macromolecules which range between 10 and 100 nm in size which consists of a core, an internal repeating unit layer and outer functional units which enable dendrimers to be polyfunctional [7,41]. Dendrimers undergo chemical synthesis via polymerization, during the formation process. Dendrimers are globular in shape and have a highly modifiable surface, which makes the nanocarrier more biocompatible and easier to degrade [7,42].

One Study performed by Khan et al. aimed to treat inflammatory lung diseases including COPD and asthma by encapsulating siRNA in poly(amidoamine) (PAMAM) and poly(propylene imine) dendrimers with a lipid substitution. The combinational approach demonstrated a synergistic effect which enabled the dendrimers to target tyrosine-protein kinase receptor, Tie-2-endothelial cells within the lung. Specifically, the PAMAM-conjugated dendrimers with C15 cholesterol tails and polyphenylene ethynylene (PPE) dendrimers with C15 and C14 cholesterol chains demonstrated high levels of potency. Additionally, the in-vivo data showed that the dendrimer-lipid compounds did not increase proinflammatory cytokines and the murine subjects did not experience weight loss from toxicity [42,43].

Vasile, E. (2014), demonstrated that Gold-PAMAM dendrimer nanocomposites exert higher antioxidant effects than Gold-cored poly(propyleneimine) (PPI) dendrimers and ascorbic acid. To compare, the Gold-PAMAM dendrimers had an 85-fold higher rate constant than ascorbic acid which potentiates the possibility of GOLD-PAMAM to be a suitable drug delivery system that selectively targets oxidative stress [44].

4.1.3. Inorganic nanoparticles

Inorganic nanoparticles are highly desirable due to their anatomical characteristics which reduce peripheral interactions during the transportation between the administration site, and the target site [41]. For example, magnetic nanoparticles are heavily influenced by the ambient magnetic field in order for it to reach the desired target site. This can occur through active or passive strategies based on the properties of the ligands bonded to the complex. Magnetic nanoparticles can be either biodegradable or non-biodegradable. This determination is influenced on the type of coating surrounding the metal core. Whilst the metal core is typically containing inorganic atoms like cobalt, gold, iron and nickel; the functional coat is utilized to reduce unintended interactions with other particles present in the environment. The non-biodegradable magnetic NPs are typically excreted by the kidneys, and this places further considerations such as toxicity to the patient and could potentially be disadvantageous [7]. Nonetheless, inorganic nanoparticles are reported to have serious cardiotoxic effects. Various experiments have indicated the penetration power of nanoparticles into alveolar capillary barrier thus entering the blood circulation and reaching systemic organs. This makes the heart a specific organ at the target of nanoparticles to get accumulated and potentially damage the heart. There are various mechanisms by which these nanoparticles demonstrate their toxic effects that include metal toxicity, damage to heart membrane, mechanical disturbance, generation of reactive oxygen generation leading to oxidative stress followed by inflammation, and mitochondrial damage and DNA damage. These serious side effects summon further investigation and the need of continuous monitoring [45].

The advantages and disadvantages of the use of inorganic NPs are further summarized in Table 1.

Table 1
Advantages and disadvantages of Nanoparticle therapies.

Nanoparticle Type	Advantages	Disadvantages
Polymer-based NPs	• Biocompatibility. • Highly stable. • Highly specific delivery system. • Required in small quantities. • High surface-to-volume ratio. • Ability to modify. physiochemical characteristics [55,56].	• Limited progress of PLGA-miRNA in COPD clinical applications due to the instability of miRNA. • Pharmacokinetic studies are required. • Have a narrow therapeutic efficacy. • Potential toxicity [1,14,55].
Inorganic NPs	• Metallic nanoparticles have received FDA and European medicines agency approval and have demonstrated to be therapeutically effective and safe in clinical studies. • Beneficial in imaging and theranostic applications [1]. • Highly feasible in industrial production [55,56].	• Concerns with elimination in non-biodegradable metallic nanoparticles. • Limitations in solubility [55,56].

5. Plant-based bioactive compound-loaded nanoparticles

Medicinal plants have provided promising therapeutic potential in the treatment of COPD. Phytochemicals (plant-derived products) have heightened research interest due to their structural diversity and historical applications in healthcare and traditional medicine systems across the world. Historically, many medicinal plants have shown to have potential in treating inflammation and respiratory diseases such as COPD, asthma, tuberculosis and bronchitis. Moreover, various phytochemicals have demonstrated antioxidative, anti-inflammatory and anti-microbial activities which make them a potential candidate for the treatment of respiratory diseases [25].

Plant extracts including Loquat *(Eriobotrya japonica),* Lotus *(Nelumbo nucifera)*, pomegranate *(Punica granatum)*, licorice root (*Glycyrrhiza glabra*), and green tea (*Camellia sinensis*) have reported antioxidant and anti-inflammatory properties which are pivotal in potentially treating lung inflammation [25,50].

The main limitation to the clinical use of phytochemicals is their poor solubility/permeability, low bioavailability, and rapid degradation. However, in recent years various drug delivery methods have been employed to enhance the delivery of these phytochemicals. Many of these nanotechnology-based therapeutic approaches; polymeric NPs, liposomal delivery, liquid crystalline NPs, micelles, and nanoemulsions are designed to increase the stability and alter the release of the plant-based bioactive drug [25,49].

Nonetheless, in conjunction to the significant studies on nano-encapsulated phytoceuticals earlier reported by De Rubis et al. [4] and Paudel et al. [25] Liu et al. (2022) studied the *in-vivo* anti-inflammatory properties of 18β -Glycyrrhetinic Acid (18β-GA) in ovalbumin-induced asthma in mice. The study demonstrated that 18β-GA significantly reduced inflammation and improved lung function in this mouse model. This occurred through a reaction where 18β-GA inhibits the ovalbumin-induced phosphorylation of the nuclear factor kappa B (NF- κB) transcript factor within the lungs of the asthma-induced mouse models. In addition, the study showed that 18β-GA increased the expression of the nuclear factor erythroid 2-related factor 2 (Nrf2) and (HO-1). The authors concluded that 18β-GA represents a viable therapeutic strategy for asthma and potentially other inflammatory respiratory illnesses. One limitation to only utilizing free 18β-GA was that its potency is dependent on the inhibition of the Nrf2/HO-1 pathway which further supports the necessity to encapsulate the 18β-GA within a suitable nanocarrier [50]. It is important to note that 18β-GA also possesses poor bioavailability and a low water solubility, which restricts 18β-GA from being utilized as a conventional therapy in clinical practice. However, encapsulating 18β-GA into advanced delivery systems has the potential to improve the bioavailability and thus be a viable option to progress this phytochemical into clinical practice.

Fig. 5 summaries various sections to present discussions in a concise manner.

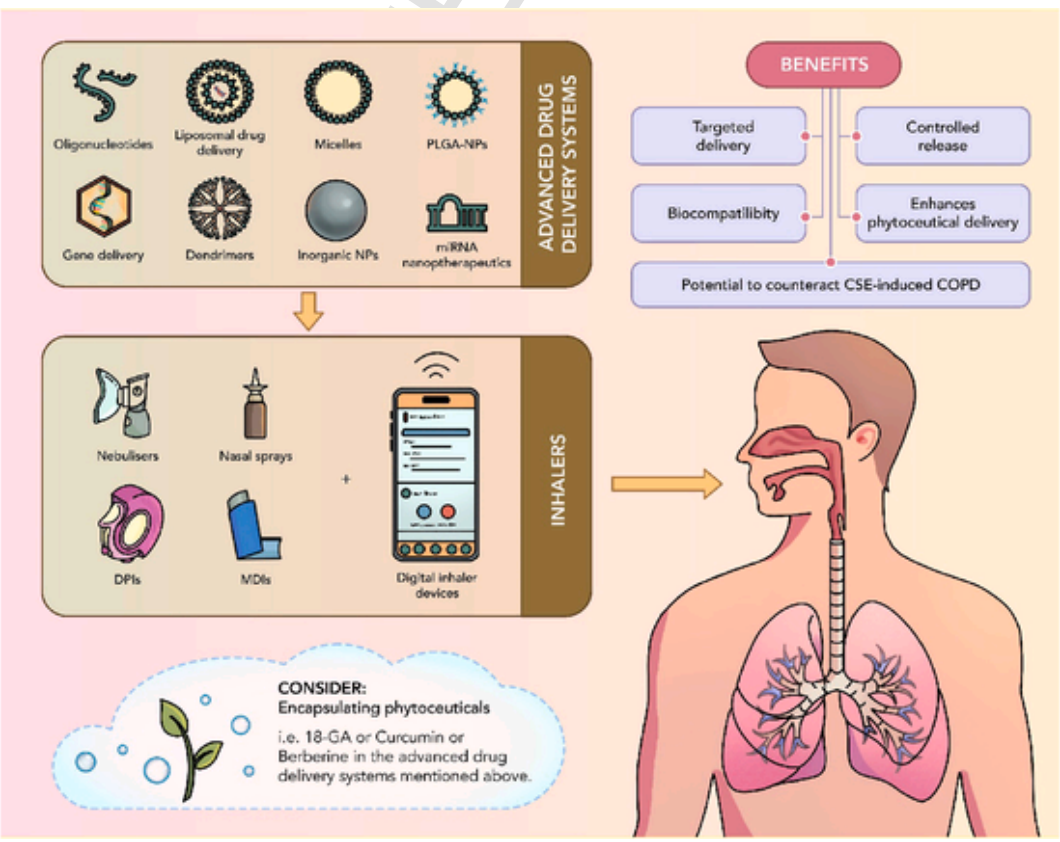

Fig. 5. A diagrammatic summary of various nanoparticles systems, their applications, role, and examples.

6. Investigational clinical studies and patents

Currently the FDA (Food and Drug Administration of USA) have several studies pending approval that employ NP-based drug delivery systems for other respiratory illnesses including lung cancer however clinical studies focusing on COPD are lacking [7]. However, overtime patents for Nanoparticles with therapeutic potential to combat COPD have been published and have been referenced in Table 2. As respiratory diseases including COPD pose a significant threat to the global population, there has been in increased desire to take NP delivery systems through the research pipeline from pre-clinical trials to launch. Whilst most NP delivery research has historically focused heavily on asthma, acute lung injury and lung cancer; more recent *in-vivo* studies are detailing the advantageous effect NPs have on managing COPD, as shown in Table 3. Vij, N. et al., 2016 utilized PEGylated immune-conjugated PLGA NPs to target neutrophils (inflammatory cells) by reducing LPS-induced inflammation and initiating lung tissue repair in obstructive respiratory states including COPD. The results reflected that within mouse models, CSE induced inflammatory marker, IL-1β and NFκB expression ($P < 0.05$) had reduced which indicated that the encapsulation of ibuprofen can mediate the protease-antiprotease-imbalance that

Table 2
Recent Patents and Patent Applications for Drug Delivery Systems which target COPD.

Patent Application number	Type of Nanoparticle	NP Size	Active Principle	Potential Application
US10034837B2	Polymeric Nanoparticle	1–500 nm	Cross linked polymeric hydrogel microparticle	COPD, Bronchial Asthma, Cystic Fibrosis, Chlorine Inhalation (poisoning) [51].
US20140186290	Polystyrene	500 nm	Polymer blend of a PLGA NP	COPD, Asthma, Bronchitis, Cystic Fibrosis [52].
US20150126589	Polyethyleneimine	1–1000 kDa	Gene Delivery	COPD, Cystic Fibrosis, lung cancer, emphysema, chronic bronchitis, pulmonary edema [53].
US20140302147	Distearoylphosphatidylcholine (DSPC) and $CaCl_2$	1–5 μm	Beta-2-agonist encapsulated in porous nanocarrier particles	Patients with respiratory illnesses including COPD [54].

Table 3
In-vivo and clinical trials in respiratory diseases which utilize NP drug delivery systems.

NCT	Active Ingredient	Advanced Drug Delivery System	Population	Indication	Key findings
NA	Nintedanib	Liposomes	Naïve mice	Pulmonary Fibrosis	An 8000 fold increase in AUC was identified when using liposomal delivery in comparison to oral free Nintedanib administration. The liposomal formulation demonstrated an enhanced efficacy of the drug with reduced side effects during in-vivo studies [59].
NC-6004	Cisplatin	Micelle	Patients over 18 years of age with histologically or cytologically confirmed stage IV squamous NSCLC	Stage IV Non-small cell lung cancer	Higher Cisplatin doses were better tolerated in patients within the study as no clinically significant indicators of neurotoxicity, nephrotoxicity or ototoxicity were observed [60].
NA	Budesonide	Liposomes	Ovalbumin-sensitised C57/Black 6 mice	Asthma	Weekly dosing of liposome-encapsulated budesonide is equally as effective as daily budesonide dosing in reducing inflammatory markers within lung tissues. Thus, reducing the frequency of dosing which improves patient compliance and drug toxicity to patients [26].
NA	Budesonide	Porous PLGA NPs	Asthma-induced Female BALB/c Mice	Asthma	A reduction to bronchial hyperresponsiveness in maurine mouse models. The controlled release behaviour exerted by PLGA NP has sparked interest of investigators as it can be used as a novel drug delivery system for a range of respiratory diseases [28]
NA	Ibuprofen	Immune-conjugated PLGA NPs (PINPs)	C57BL6 inbred mice (16 weeks of age) with LPS-induced lung inflammation	COPD	Ibuprofen encapsulated in PINP demonstrated to be a viable formulation in reducing neutrophilic inflammation [40].
NA	siRNA	PAMAM dendrimers	Female Swiss CD-1 outbred mice aged 6–8 weeks	Asthma, COPD, interstitial pulmonary fibrosis.	Pulmonary administration of SiRNA-containing PAMAM dendrimers demonstrated greater inhibition of TNF-in comparison to free siRNA [61].
NA	Grape seed extract (GSE) containing proanthocyanidins	Solid Lipid NPs	C57B1/6 male mice	Chronic respiratory diseases (ie. COPD)	GSE-encapsulated solid- lipid nanoparticles demonstrated greater antioxidant for greater durations of time in comparison to free GSE in mice models [62].
NCT04894409	NA	Silver NPs (AgNPs)	Male and Female healthcare workers that work at Tijuana Hospital, Mexico within high COVID-19 risk areas.	COVID-19 prevention	AgNPs demonstrated its ability to prevent the spread of COVID-19 across healthcare staff who were exposed and interacting with COVID-19 patients [63].

occurs in COPD [40]. Comparatively, Bohr, A. et al., 2020, studied siRNA, antisense oligonucleotides and miRNA as therapeutic strategies to target acute lung inflammation in murine models. Generation 3 PAMAM dendrimers were utilized to transfect siRNA into female swiss CD-1 mouse models with LPS-induced lung inflammation. The results demonstrated that dendriplexes with TNF-α siRNA exhibited a higher reduction in TNF-α expression at t = 4 than non-complexed TNF-α siRNA. However, it was noted that at t = 72 h, the performance of dendriplexes with TNF-α siRNA had reduced which suggests that more frequent administrations may be required [61]. Another in-vivo study conducted by Castellani, S et al., 2018, encapsulated grape-seed derived proanthocyanidins in solid lipid NPs to target the oxidative and inflammatory features of chronic respiratory illnesses. The results demonstrated that the biocompatible NP-complex reduced ROS production and NFκB expression. Moreover, the encapsulation of the phenolic compound enabled the above mentioned therapeutic actions to be efficacious for extended time periods [62].

7. Digital Inhalers (DIs): Digital inhalers are also known as smart inhalers e.g. smart pressurized metered dose inhalers. Although these devices are available for over two decades it is not until recent their popularity started to rise and have become an important aspect of e-health for asthma and COPD management [64]. These inhalers are programmed to collect data on adherence, thus allowing tailored outcomes for the management of asthma and COPD by the patient. This further improves inhaler adherence and use leading to reduced aggravation of symptoms, improved technique of inhaler uses and pulmonary function. Nonetheless, healthcare provider can tailer dose based on the data from digital inhalers on associated patterns of the inhaler use to improve clinical decision-making, and clinical care. However, improved technological skills of the patients and further studies are required to establish unanimous acceptability amongst end-users with cost-effectiveness [65]. Some examples of commercially available the DIs are; Hailie®, Adherium, Respiro® etc.

The advantages and disadvantages of different types of inhaler devices in asthma and COPD are summarized in Table 4.

7. Future directions

NP-based drug delivery systems have shown promise in managing and potentially treating COPD with higher levels of safety and precision in comparison to conventional COPD treatments. Whilst there are many desirable characteristics with utilizing NPs in therapeutics, a limitation is presented by dose-dependent toxicity and associated side effects. This can potentially result from particle size reductions and an increase in reactive surface area. Future research should be tailored to assess how different NP react to different environmental conditions to ensure safety in prospective patients. Furthermore, an increase chemical reactivity due to physical properties like surface area modifications may increase the risk of oxidative stress, inflammation and damage to genetic material, thus contributing to toxicity. Moreover, in the case of non-biodegradable metal NPs, it is critical to evaluate the level of toxicity as the elimination of the agent has the potential to impair kidney functionality. Consequently, further research is required to assess the associated long-term risk for these advanced therapeutic applications and identify which NP drug delivery systems are appropriate for specific population groups with varying severity of COPD.

8. Conclusion

Nanomedicine has paved an innovative era for potentially treating COPD. Nanotechnology has proven to be highly desirable in its ability to create novel and advanced drug delivery systems which enable an elevated level of precision when delivering the drug to the target site. Moreover, nanotechnology permits a precise and controlled dose where there is a possibility of reduced frequency of administration. Overall, NP-based drug delivery systems, will definitely improve the quality of life for COPD patients with lesser side effects in comparison to currently available drugs in the market. However, more clinical studies will need to be conducted to understand the full therapeutic potential nanoparticles have in treating COPD.

Data availability statement

This article is a review article and hence no data was used for the research described in the article.

Uncited References

CRediT authorship contribution statement

Victoria Jessamine: Writing – review & editing, Supervision, Conceptualization. **Samir Mehndiratta:** Writing – review & editing, Supervision, Conceptualization. **Gabriele De Rubis:** Writing – review & editing, Supervision, Conceptualization. **Keshav Raj Paudel:** Writing – review & editing, Supervision, Conceptualization. **Saritha Shetty:** Writing – review & editing, Supervision, Conceptualization. **Divya Suares:** Writing – review & editing, Supervision, Conceptualization. **Dinesh Kumar Chellappan:** Writing – review & editing, Supervision, Conceptualization. **Brian G. Oliver:** Writing – review & editing, Supervision, Conceptualization. **Phillip M. Hansbro:** Writing – review & editing, Supervision, Conceptualization. **Kamal Dua:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Table 4
Advantages and disadvantages of different types of inhaler devices in asthma and COPD [66,67].

Inhaler type	Inhaler Formulation	Metering system	Brands available	Upside	Downside
Pressurized metered-dose inhalers (pMDI) and can be further categorised in two categories: 1. Manual Pressurized Metered Dose Inhaler 2. Smart Pressurized Metered Dose Inhaler[a]	Inhalers consist of propellant in which a drug is either suspended or dissolved	Consists of a metering valve and a reservoir	Flovent HFA® Symbicort® etc.	Very compact thus easy to carry, rapid delivery, and with proper training, most of COPD patients can achieve the slow inhalation flow needed for pMDI.	Not breath activated/actuated. Geriatric patients with may find it difficult to actuate a pMDI device owing to poor grip and strength. A pMDI may lead to reduced doses of drug reaching the lungs if not handled properly. Cause "cold Freon" effect as pMDIs contains propellants.
Metered-dose inhalers (MDI) + spacer	Inhalers consist of propellant in which a drug is either suspended or dissolved.	Consists of a metering valve and a reservoir	e.g. Able Spacer®, Fluspacer®, AeroChamber Plus® etc.	Easy installation and use. Due to spacer, lesser oropharyngeal deposition of the drugs thus avoiding the "cold Freon" effect. Have high lung deposition of medicament compared to a pMDI.	Not as compact and portable as a pMDI and geriatric patients may find it difficult to assemble. Assembling time hinders its immediate readiness for usage. The additional cost to the medical system is another major disadvantage.
Breath-actuated metered-dose inhaler (baMDI)	Inhalers consist of propellant in which a drug is either suspended or dissolved	Consists of a metering valve and a reservoir	e.g. Easi-Breathe®	Very compact thus easy to carry, rapid delivery. Multidose device. For actuation, requires a very low inhalation flow rate (~27 L/min) which COPD and geriatric patients can easily achieve along with those suffering arthritis. Prevents contamination.	The drugs that can be effectively formulated for baMDI limits its use currently. Causes "cold Freon" effect like pMDIs.
Dry-powder inhaler (DPI)	Micronized drug blend in carrier lactose.	Blisters, Capsules, and multidose blister packs etc.	e.g. Accuhaler®, Easyhaler®, Neohaler®, etc.	Very compact thus easy to carry. Ease of use of high resistance even while exacerbating as do not need much strength. No propellants used.	Need to maintain a minimum inspiratory flow thus, may not be advisable for emergency need. Impairment of cognitive functions in COPD and geriatric patients limit their use in this population. As DPIs contain powered drug, most of them are moisture sensitive.
Nebulizers	Consist of drug in an aqueous solution or as a suspension.	A reservoir chamber having nebules dispensed via nebulizer	e.g. Jet nebulizers, ultrasonic nebulizers etc.	Several benefits as all it takes is regular breathing without any specific technique. Have facemasks that can be used easily by geriatric, pediatric and patients with altered consciousness. Can aerosolize high doses of drugs which can not be achieved with either DPIs or pMDIs. Better clinical outcomes than pMDI or DPIs.	May not be superior to other forms for COPD maintenance therapy. Some nebulizers such as jet and ultrasonic type need an outside energy source. Longer treatment times and needs daily cleaning to minimize the risk of bacterial contamination. Expensive.
Soft mist inhaler (SMI)	Consist of drug in an aqueous solution or as a suspension.	Reservoirs or Blisters of unit dose	e.g. Respimat®	Very compact thus easy to carry Multidose device. The extended duration of aerosol formation enhances the coordination of inhalation and device actuation. Smaller doses are required to get similar efficacy and safety e.g. a bronchodilator delivery using SMI and pMDI. No propellants are used.	The metered volume of 15 μL limits the dose-delivery capacity of the marketed design to drugs with adequate solubility with respect to the required dose. The administration of tiotropium via Respimat® may be avoided in patients with pre-existing cardiovascular comorbidities.

[a] discussed under section digital inhalers.

Declaration of competing interest

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

Dr. Keshav Raj Paudel is co-author and also an associate editor of Heliyon.

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