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Nanostructures for drug delivery in respiratory diseases therapeutics: Revision of current trends and its comparative analysis

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ABSTRACT

Respiratory diseases are leading causes of death and disability in developing and developed countries. The burden of acute and chronic respiratory diseases has been rising throughout the world and represents a major problem in the public health system. Acute respiratory diseases include pneumonia, influenza, SARS-CoV-2 and MERS viral infections; while chronic obstructive pulmonary disease (COPD), asthma and, occupational lung diseases (asbestosis, pneumoconiosis) and other parenchymal lung diseases namely lung cancer and tuberculosis are examples of chronic respiratory diseases. Importantly, chronic respiratory diseases are not curable and treatments for acute pathologies are particularly challenging. For that reason, the integration of nanotechnology to existing drugs or for the development of new treatments potentially benefits the therapeutic goals by making drugs more effective and exhibit fewer undesirable side effects to treat these conditions. Moreover, the integration of different nanostructures enables improvement of drug bioavailability, transport and delivery compared to stand-alone drugs in traditional respiratory therapy. Notably, there has been great progress in translating nanotechnology-based cancer therapies and diagnostics into the clinic; however, researchers in recent years have focused on the application of nanostructures in other relevant pulmonary diseases as revealed in our database search. Furthermore, polymeric nanoparticles and micelles are the most studied nanostructures in a wide range of diseases; however, liposomal nanostructures are recognized to be some of the most successful commercial drug delivery systems. In conclusion, this review presents an overview of the recent and relevant research in drug delivery systems for the treatment of different pulmonary diseases and outlines the trends, limitations, importance and application of nanomedicine technology in treatment and diagnosis and future work in this field.

1. Introduction

Pulmonary diseases still remain a critical challenge for actual therapy, according to the report of Heron [1] by the end of 2017 in the United States, chronic lower respiratory diseases and influenza-pneumonia keep a place between the 10 leading causes of death, with a 5.7% and 2.0% of the total deaths per year, respectively. And this situation can get worse in the case of developing countries, where respiratory infections can be found leading the list of the principal causes of death [2]. Regardless of the number of advances in medicine and development of new treatments, their efficacy in different numbers of pulmonary diseases is still limited [3].

There are a wide range of respiratory diseases and disorders that can vary between chronic, viral infections, fungal and bacterial infection and cancer. Between the historically relevant pulmonary diseases can be found tuberculosis (TB) still having approximately 10 million cases reported by the year of 2017 with a rate of reduction in new cases of 1.5% per year [4], in spite of this reduction in annual cases the actual treatment for latent TB remains a challenge for medicine [5]. It is well known

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List of abbreviations

COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DDS	drug delivery systems
DTX	docetaxel
HIV-1	human immunodeficiency virus 1
LBNPs	lipid-based nanoparticles
MERS-CoV	Middle East respiratory syndrome coronavirus
NLCs	nanostructured lipid carriers
NSCLC	non-small cell lung cancer
PAMAM	polyamidoamine
PCL	poly(caprolactone)
PEG	polyethylene glycol
PEOz	poly(2-ethyl-2-oxazoline)
PGA	poly(glycolic acid)
PLA	polylactid acid
PLGA	poly lactic-*co*-glycolic acid
PNPs	polymeric nanoparticles
PTX	paclitaxel
PVP	poly(N-vinyl pyrrolidone)
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SLNs	solid lipid nanoparticles
TB	tuberculosis
TFFD	thin-film freeze drying

that the multidrug-resistant Mycobacteria strain represents the leading cause of the current antimycobacterial-drug crisis in the healthcare system. In this context therapy using nanoparticles has become of vast interest due to the potential to overcome the drug resistance. Multiple studies have demonstrated the efficiency of different nanostructures to treat TB [6–8]. For example, functionalized biodegradable polymers have been used to trap silver nanoparticles achieving a synergy effect to induce cytotoxicity on host cells, also this composite can function as a nanocarrier to deliver drugs used in therapeutics against TB infection. Another example with a functionalized biopolymer is the use of Curdlan nanoparticles conjugated to cyclodextrin. Curdlan possesses immunomodulatory effects and anti-infective properties since it is recognized by dectin-1, a receptor expressed on macrophages. Thus, intracellular release of drugs into macrophages is successfully achieved. In the same manner, *in vivo* studies with a mannose-modified macrophage-targeting solid lipid nanoparticle loading isoniazid showed improved aggregation of macrophages on the surface of the airway and increased uptake and enhanced intracellular antibiotic efficacy [9]. These and other studies imply that nanostructures have remarkable potential for the treatment of TB. Their primary advantages of nanostructures such as long shelf life, dipping of dosing frequency, and enhancement of drug bioavailability make them more convenient. Hence, the success of the use of nanostructures will depend on the toxicological profiles linked with understanding the fate of polymeric components of nanocarriers in the body along with the clinical outcome.

Lung cancer is also a challenging respiratory disorder. Lung cancer is the most common cancer worldwide, accounting for 2.1 million new cases and 1.8 million deaths in 2018 according to the World Health Organization. Despite the great advances in lung cancer treatment such as surgery and radiotherapy, these approaches are highly expensive, while chemotherapy can be elected when tumor size limits surgical resection, chemotherapy presents great toxicity and poor targeting, additionally, the presence of drug resistance is a complex challenge in cancer therapy [10,11]. Thus, biomedical research through cutting-edge technology is working to find functional, more effective, and less expensive therapies that may cause fewer side effects than conventional treatments such as radiotherapy and chemotherapy.

In recent years, respiratory viral infections have gained worldwide health concern. In 2012, the first case of MERS-CoV (Middle East respiratory syndrome coronavirus) was reported in the Kingdom of Arabia Saudi, and up to now, the majority of the cases were reported in the Middle East, however, patients with MERS-CoV have been also found in Europe, Asia and North America [12]. MERS-CoV provokes a severe respiratory disease which has reached a global fatality rate around 32%, while Middle East and Africa are the regions with the higher fatality rates for this disease, 32.7% and 83.3%, respectively [13]. According to the documented cases of MERS-CoV patients present symptoms like cough, fever, rhinorrhea, nausea, vomiting, fatigue and myalgia. But severe cases can develop respiratory failure. Up to now there is no reported efficient treatment for MERS and the treatment consists in antipyretic drug administration, maintenance of hydration and respiratory support [14].

Coronavirus disease 2019 (COVID-19), caused by a strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing pandemic initiated in late December 2019, when the first case of SARS-CoV-2 was reported in Wuhan, China. Since then, COVID-19 has spread around the world. On January 30, 2020, the World Health Organization (WHO) declared a global health emergency and shortly after declared the COVID-19 outbreak a global pandemic [15].

As SARS and MERS are caused by coronaviruses, infected people develop similar symptoms that range from mild cold-like symptoms to severe symptoms such as pneumonia and severe pulmonary disorders. Although its similarities, MERS-CoV has shown a higher mortality rate (35.37% of the confirmed cases) but lower transmission rate, in comparison to SARS-CoV-2 that shows a lower mortality rate (2.34% of the worldwide confirmed cases) but with higher transmission rate [16]. On August 23, 2021, the U.S. Food and Drug Administration (FDA) approved the first COVID-19 vaccine and various vaccines for COVID-19 have emergency use authorization, also several countries have approved mass vaccination, however, to ensure global vaccination, efficient planning and logistics will be required [17]. Furthermore, the MERS-CoV vaccine is still in development and the time for this vaccine development is estimated for at least 10 years [18]. Notably, no prophylactic or therapeutic interventions of proven efficacy for SARS-CoV-2 and MERS-CoV are currently available. Therefore, finding therapies for these diseases, and especially for COVID-19 is a critical need [19].

In the treatment of lung diseases, the inhalation route is frequently used to administer drugs. Among the advantages of the inhalation route are higher efficiency (high pulmonary concentrations of the drug can be achieved), decrease of the therapeutically effective dose, and lower side effects (low systemic drug concentration). Furthermore, the inhalation route has been studied as a non-invasive route for systemic delivery of drugs [20]. However, administration of drugs by inhalation route has several limitations including non-specificity of the active agents, low efficiency, and short times of active agent release which must be addressed to prevent secondary adverse effects [21].

The use of nanostructures in the pharmaceutical field can provide new tools that can help to maintain the properties of active agents that its stand-alone stability and solubility under physiological conditions is poor, also by conditioning the release of drug only under specific conditions with an extended window of drug release achieving and smart and controlled release into the specific site of action [22]. The nanostructures used in pharmaceutical field are known as drug delivery systems (DDS), and between the main characteristics of this type of structures is that at nanoscale usually can be obtained a longer circulation time and facilitates the cellular uptake, which can be transduced into an increased bioavailability of drugs. For that reason,

nanotechnology has gained great interest in the past decades for drug delivery, the potential benefits of the use of nanostructures is the possibility of developing targeted therapies for certain diseases.

Considering the relevance of pulmonary diseases for the global health burden, and the necessity of finding more effective treatments for historical and newly appearing diseases, it seems natural to take advantage of drug delivery nanotechnology to generate better pulmonary therapies. In consequence, the present review is focused on the analysis of work done in nanotechnology applied to pulmonary therapeutics, identifying the main nanostructures used in the respiratory system, the differences and opportunities, not only in fabrication methods but also the smart integration of new materials.

The nanostructure size determines lung tissue penetration and its residence, i.e. the mucus layer is permeable to particles sized in the range of 60–500 nm showing faster diffusion rates for smaller size of nanoparticles, which can be desirable or not depending on the interest of maintaining the drug in the pulmonary epithelium (i.e. in lung cancer, epithelial cells are affected, the interest is maintaining the chemotherapeutics in the epithelial surface in order to keep the healthy tissues and organs unaffected). Extensive attention has received the use of the respiratory route for systemic non-invasive administration of different drugs and vaccines due to the reduced metabolism compared with intravenous and oral routes. In section 2, the methodology to define the scope of research work is described. Then, The details will be discussed in section 3. Besides the size particle, materials of nanostructures play a critical role in its application for pulmonary therapeutic use. Different properties can be found in nanoparticles that are material-dependent, such as biocompatibility, clearance, and degradation rates, releasing profiles, loading capacity, toxicity, and its ability to sort different biological barriers. Modification and combination of distinct materials represent a useful tool to obtain more efficient drug delivery systems. For instance, metal nanoparticles are used for cancer diagnosis and photothermal therapy, likewise polymers are promptly used for drug delivery systems (examined in section 4). Then, in section 5, the main challenges found in the clinical translation for drug delivery nanostructures during its preclinical and clinical phases of development, and listing recent clinical trials of drugs focused in respiratory diseases treatment. In section 6, challenges that must be considered when pulmonary drug delivery is attempted are discussed, especially in nanostructure properties that will define the interaction with different biological and physical barriers in the respiratory tract. Finally, section 7 and 8 correspond to discussion and conclusions, respectively.

2. Review methodology

In this review, to analyze the trends in drug delivery for different nanostructures, a revision using the database ScienceDirect and the meta searcher Google Scholar. Using the keywords: “drug delivery”, “nanostructure”, “respiratory diseases”; in combination with common names for drug delivery nanostructures (i.e. “polymeric nanoparticles”, “micelles”, “dendrimers”, etc.), the most relevant research articles for each type of nanoparticles from the year 2018 to the present (2021) were selected. Articles selected were focused on the treatment of different respiratory diseases such as asthma, lung cancer, different types of infections (e.g. viral and bacterial) among others. Despite the main objective was to identify treatments administered by inhalation route, some relevant work in lung treatment using nanostructures by other administration vias was collected too depending on the criteria of the authors due to the possibility to translate into an administration by inhalation route.

Results obtained from ScienceDirect search are resumed in Table 1 the first column shows the searching equation, the number of results obtained are presented in the second column as Research Articles, while the third column presents the number of review articles found, these results were collected on March 9th, 2021.

Table 1
Keywords used to search current publications using ScienceDirect.

Nanostructure	Searching equation	Research articles	Review Articles
Polymeric nanoparticles	(“polymeric” OR “polymer”) AND “nanoparticles” AND “drug delivery” AND "(respiratory diseases” OR “lung diseases")	43	15
Polymeric micelles	(“polymeric” OR “polymer”) AND “micelles” AND “drug delivery” AND "(respiratory diseases” OR “lung diseases")	39	15
Liposomes	“liposomes” AND “drug delivery” AND "(respiratory diseases” OR “lung diseases")	20	7
Lipid based nanoparticles	(“nanostructured lipid carrier” OR “solid lipid nanoparticles”) AND “drug delivery” AND (“respiratory diseases” OR “lung diseases")	8	1
Dendrimers	“dendrimers” AND “drug delivery” AND (“respiratory diseases” OR “lung diseases")	3	1
Exosomes (Extracellular vesicles)	(“exosomes” OR “extracellular vesicles”) AND “drug delivery” AND (“respiratory diseases” OR “lung diseases")	4	9

3. Inhalation as a route for drug delivery

There are various routes of administration available, each of which has associated advantages and disadvantages. The route by which drugs enter the body has an impact on drug onset of action, the duration of that action, the bioavailability, and the intensity of the effect [70]. It was proposed by Boroujerdi to classify the administration routes into four categories; the first category consists of administration routes that enable the drug to contact various organs, and these organs can provide either local or systemic actions, four subgroups fall into this category and all of them present a biological barrier. Some examples are sublingual, pulmonary, intramuscular and rectal routes; the second category includes administration routes that avoid biological barriers by administering drugs directly into the circulatory system (i.e., intravenous injection); in the third category drugs are administered topically, the active compound must diffuse through the stratum corneum making the biological barrier in this route more complex compared with the first category route, local and systemic actions are achieved depending on the properties of the drugs and the environmental conditions and ultimately modify the absorption process. The fourth category consists of a wide variety of administration routes created to have localized and targeted action, however, drugs can access the circulatory system and present systemic effects [71]. Fig. 1 shows a graphic representation for administration routes of the previous categories presented.

Inhalation route (first category group B, Fig. 1) is historically the most common route for the treatment of pulmonary diseases and respiratory tract disease, especially for the treatment of lung infection, asthma, and COPD because the drugs can easily reach the site of action without much interaction with the rest of the organism [72].

3.1. Nanoparticle pharmacokinetics

The pharmacokinetics of nanoparticles provides a greater understanding of the clinical outcome and knowledge to minimize side effects. Nanoparticles that function as pharmaceutical drugs must be metabolized or excreted from the body after their intended medical use, as required by the FDA.

When nanoparticles are administered intravenously, they circulate in the bloodstream and then cleared and excreted from the body by renal and hepatobiliary elimination. However, it is important to note that the IV route comprises multiple limitations such as risk of infection,

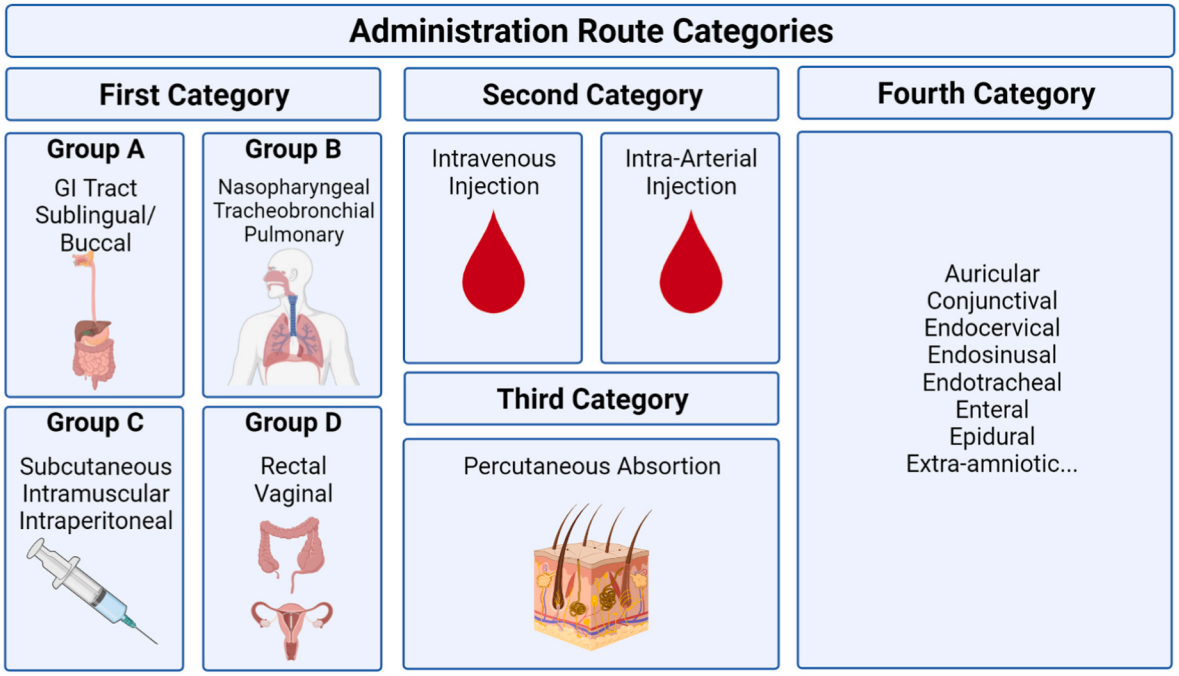

Fig. 1. Administration routes organized following the Bojourdi classification, first category have in common a "simple" biological barrier; the second category avoid biological barriers and the drugs are administered directly into the circulatory system; the third category represents the most complex barrier (skin, especially the *stratum corneum*); and in the fourth category, some examples of specialized routes for local drug delivery.

possibility of embolic phenomena, it is painful, among other disadvantages. For these reasons, lung-based drug delivery of nanoparticles is receiving increased attention due to the large surface area available, the thin epithelial barrier, and a large contact with the circulatory system and circumvention of the first pass effect. Also, the respiratory system presents lower enzymatic activity when compared to other organs, reducing the hepatic metabolism of drugs [73].

The lung possesses pulmonary-specific pharmacokinetic processes, including: deposition and clearance (A general scheme of particle deposition, elimination and clearance paths are presented in Fig. 2). (1) Following inhalation nanoparticles travel along the respiratory tract where they can suffer deposition in the different regions of the lungs,

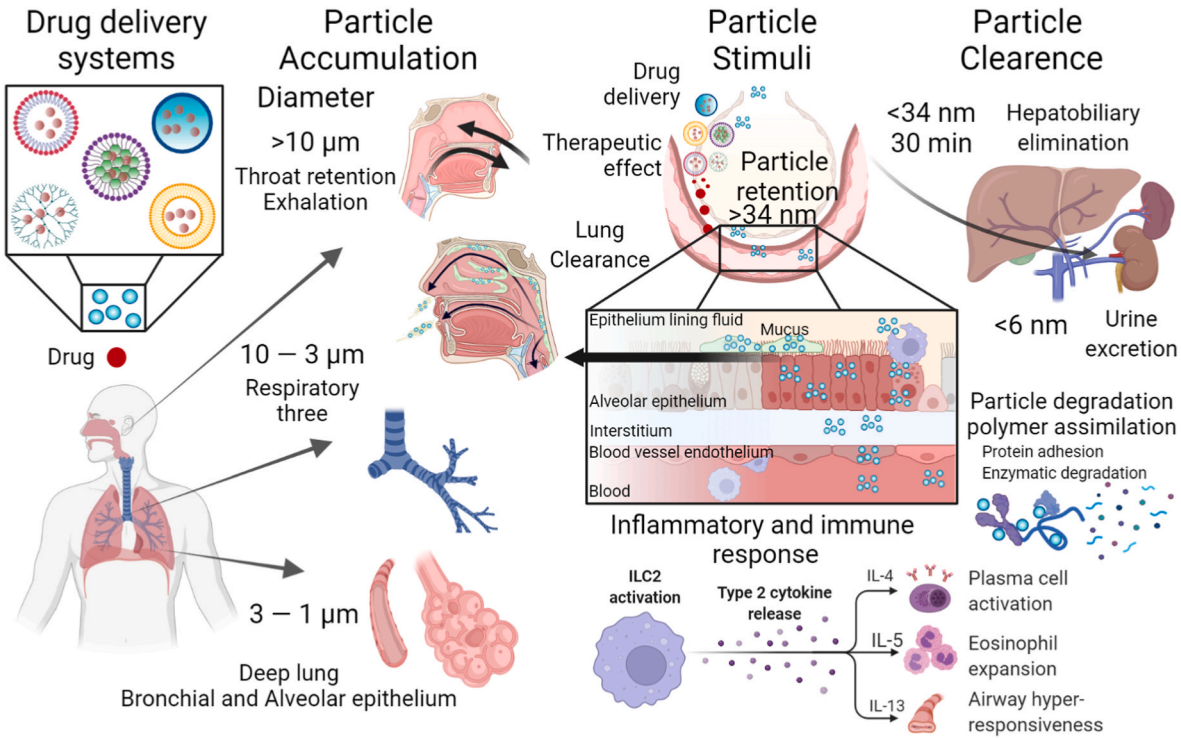

Fig. 2. Cell interactions and pathway activation due to nanoparticle presence. Particle fate is mainly determined by particle size due to hydrodynamic diameter and its aerodynamics. Each case is represented by sections from upper to lower airways.

this deposition depends on inhalation flow, device characteristics, but mainly depends on the particle size of the formulation, for example, particles over 10 μm will tend to impact the initial parts of the throat and most of the particles will not reach the deep lungs, while particles between 1 and 3 μm easily reach the deepest part of the lungs [74]. Particles unable to reach the lung and deposit in the mouth-throat region are subsequently swallowed [75,76]. The nanoparticles that reach the lung but fail to deposit are exhaled [77]. (2) Nanoparticle clearance from the lung involves absorptive (dissolution) and non-absorptive (physical) mechanisms. In general, nanoparticles between 35 and 6 nm size are accumulated and particles smaller than 6 nm reach the urinary system faster [78,79]. For other promising nanoparticles larger than 6 nm it is proposed that the elimination process involves the hepatic clearance route, such as liver, bile and intestine [79,80]. When it comes to poorly-soluble particles in the respiratory tract, physical mechanisms seem to be the main clearance mechanism, which include macrophage engulfment, transport and mucociliary forward motion towards the oropharynx. Mucociliary clearance is the primary innate defense mechanism of the lung, the mucous layer and the cilia on the surface of ciliated cells act as a protective layer to trap and clear the particles in the upper airways. However, in the deeper areas of the lungs, i.e., the alveolar region, the transport mechanism is complex. One of the predominant mechanisms of clearance is through alveolar macrophages. Finally, it is important to consider that nanoparticle pharmacokinetics is an elaborate process that is influenced by drug formulation, particle size, particle physicochemical characteristics, type of device, and patient-related factors [81].

4. Nanostructures on respiratory therapy

Nanomedicine is a promising field and relatively new, it proposes that the combination between nanotechnology and biological systems can obtain new interactions that can be further exploited when compared with microscale materials [82]. Specifically, in terms of drug delivery, nanomedicine is promising that the use of nanomaterials can improve the delivery of poorly soluble drugs in water, targeted delivery, and long releasing of drugs, and in general term improve the overall drug performance [83].

There exist a variety of nanostructures used for drug delivery purposes, these nanostructures can vary in shape, size, and material used. The variation between those variables can modify the behavior and functionalities of the structure within the biological environment, the drug that the structure transports, so the materials used can be combined to improve the structure's properties [84]. In the next sections are mentioned some of the most used nanostructures for drug delivery. A summary of most nanostructures is presented in Fig. 3.

4.1. Polymeric nanoparticles (PNPs)

Polymeric nanoparticles (PNPs) consider two types of structures, nanospheres that are dense polymeric matrices where the drug is supported within the matrix and nanocapsules that are hollow and the drug is contained inside the matrix, they can vary from 5 to 1000 nm, even when the range of obtained PNPs vary from 100 to 500 nm [85]. PNPs are one of the most preferred drug delivery structures due to their desirable characteristics such as high encapsulation efficiency, biocompatibility, and efficacious delivery of macromolecule drugs [86]. Some techniques to increase the circulation time of polymeric nanoparticles have been proposed to use different modifications on particle size, shape, and surface [87]. Commonly used polymers for PNPs fabrication are poly lactic-*co*-glycolic acid (PLGA), polyglycolide or poly (glycolic acid) (PGA), polylactic acid (PLA), polyethylene glycol (PEG), and some natural biodegradable polymers like chitosan and hyaluronic acid-based polymers [88]. There exist a variety of techniques for PNPs fabrication, every technique can influence the properties of the final structure, but also relies on the polymer used properties; solvent evaporation, nanoprecipitation, salting-out, nanoemulsion, and interfacial polymerization are the most common techniques used [89]. Fabrication and some representative illustrations are presented in Fig. 4.

PNPs have been widely investigated for the treatment of respiratory diseases; in gene therapy, improving pDNA delivery using PEG surface-modified nanoparticles in simulated pulmonary epithelium obtaining an enhanced and sustained release up to 14 days [90], or varying the PNPs composition to study its effectiveness delivering different biological agents [91]. Loading PNPs with antibiotics to treat drug-resistant infections is a common topic, especially for the case of cystic fibrosis patients where the mucus layer has difficulties on free drug reaching the bacteria [92,93], or loading particles with antiinflammatory agents to improve the treatment pulmonary inflammatory diseases [94], and even improving common therapy on asthma symptoms treatment [95]. Also explored in the treatment of pulmonary cancer by loading with different chemotherapy agents [96]. And some others have investigated how the properties of PNPs can modify their efficacy, such as the interaction of particle size and cellular uptake [97], providing coatings to the PNPs to enhance the interaction with lung barriers [98], or exploring the effects of the manufacturing process in PNPs characteristics for pulmonary delivery [99].

Overall, to date, the process of obtaining PNPs is in the process of evolution, where it should be based on methods of good reproducibility and considered safe for the organism [100]. In addition, PLGA nanoparticles have been used in the treatment of asthma. During this research the nanoemulsion method was used to obtain PLGA nanoparticles coated with chitosan for the use of low doses and low frequency of the drug budesonide [101]. On the other hand, Dong et al. [102], report trials of chitosan-coated PNPs for the treatment of chronic obstructive pulmonary disease, and pulmonary infection using a solvent evaporation method. In another study using the solvent displacement method nanoparticles loaded with docetaxel (DTX) were obtained for lung cancer treatments [103]. Nowadays one of the respiratory diseases of the latest importance is the MERS-CoV [104] has prompted the Basha development of new methods of obtaining PNPs [105]. Double emulsion process method in the generation of PLGA-based hollow nanocarrier with cyclic diguanylate monophosphate for MERS-CoV and thus providing a positive viewpoint in vaccine development [31]. An extended summary of the most relevant research is listed in Table 2.

4.2. Polymeric micelles

Polymeric micelles are composed of a two-layer structure; they have an internal core provided by the hydrophobic part of the block copolymer; and the outer shell also called "corona", formed by the hydrophilic part of the block copolymer [106]. Micelles have interesting properties for drug delivery such as a) a hydrophilic coat around the internal core that can improve the solubility of poorly soluble water drugs and protect the drug inside from degradation, b) a size from several tens of nanometers with a narrow distribution that difficult the renal excretion, c) and a biocompatible polymer shell that increments the time of blood circulation for micelles [107]. The most used polymer for the micellar corona is the PEG, but also poly(N-vinyl pyrrolidone) (PVP), poly(2-ethyl-2-oxazoline) (PEOz), and phosphocholine-based polymers have been used for the hydrophilic corona. While the inner hydrophobic core is usually composed of PLA, poly(caprolactone) (PCL), and some others like polycarbonates and poly amino acids [108]. Polymeric micelles fabrication and schemes are presented in Fig. 5.

Polymeric micelles have been specially studied for the treatment of lung cancer trying to improve drug targeting and reducing the side effects of conventional cancer chemotherapy [109–111], and exploring the increased targeting of micelles by modifying the surface to interact with tumor microenvironment conditions such as pH [112] or peptide targeted of the micelles tested in a pulmonary melanoma metastasis model [113]. Also was explored the loading of the micelles with different drugs e.g. antifungal agents to treat lung fungal infections with

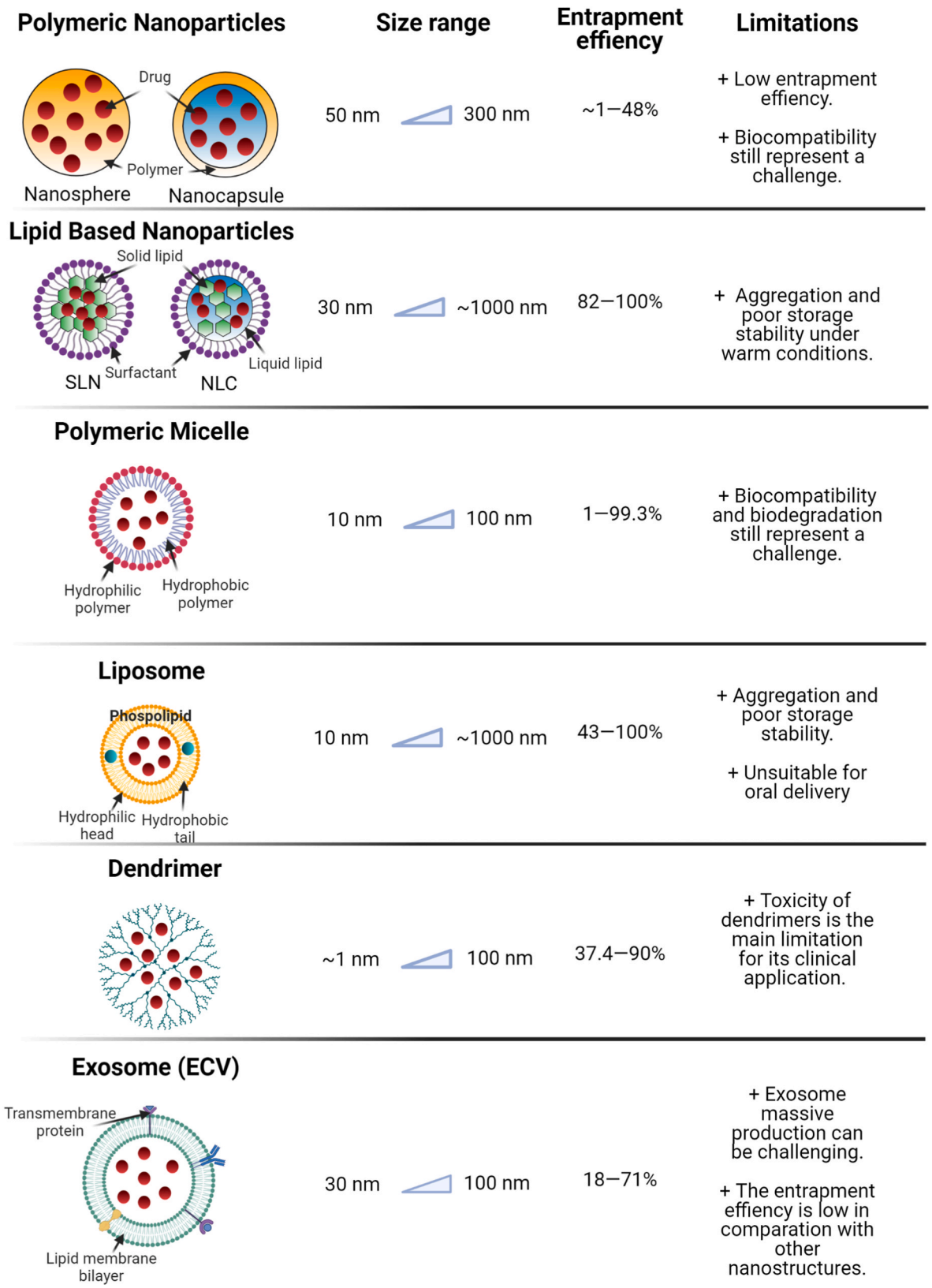

Fig. 3. Common nanostructures for drug delivery. Solid Lipid Nanoparticle (SLN); Nanostructured Lipid Carrier (NLC); Nanoparticle (NP); Extracellular Vesicle (ECV).

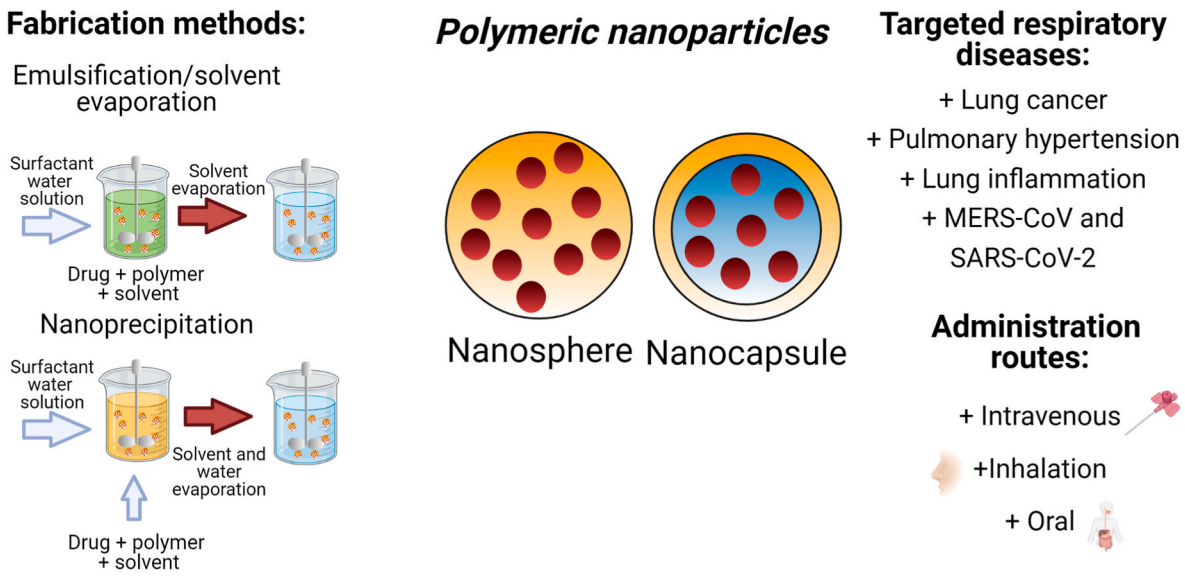

Fig. 4. Common fabrication methods, focusing on diseases and administration routes of polymeric nanoparticles in the treatment of respiratory diseases.

reduced side effects [114], or loading peptide-modified micelles with fasudil for pulmonary arterial hypertension aiming to increase the retention time of micelles in affected arterial cells [115]. Additionally, in recent years, polymeric micelles were studied in the gene therapy field by focusing on the efficiency of delivering genes and drugs in combination for the treatment of acute pulmonary inflammation that can be provoked by severe injury in the lungs [116]. Some studies were made to better understand how micelles interact with pulmonary epithelial cells, establishing the processes of cellular uptake for inhaled micelles, and the biodistribution of those types of particles [117,118].

The incorporation of multiple drugs it's an important way against respiratory diseases [119]. As a result, many authors had proposed some methods, one of them for treatment of prevalent and deadly small cell lung cancer using thin-film method to obtain drug-loaded polymeric micelles with cisplatin obtained good results [120]. In another study against non-small cell lung cancer (NSCLC) the polymeric micelles were prepared by film hydration method loaded with DTX (hydrophobic drug) showing favorable drug delivery [121]. Besides, Muddineti et al. [122], in their study made cholesterol-grafted chitosan micelles as nanocarriers with a dialysis method. It is a fact that conventional treatments tend to have certain limitations for the development of polymeric micelle, in a recent study the optimization of polymeric micelles was proposed, the structure of PEG and PCL was used with the nanoprecipitation method, the result was a high drug loading capacity [123].Thus, in the case of cancer treatment, studies with different nanostructures have shown particular advantages, for example, micelles have been widely used as carriers of lipophilic molecules due to their high biocompatibility, they can be easily designed to adapt to different environments, and they can be functionalized with antibodies. Likewise, liposomes are vastly biocompatible and stable, protecting contents from degradation. Polymeric nanoparticles are highly stable in the gastrointestinal environment and allow controlled drug release. They can be functionalized for targeted delivery. Chitosan nanoparticles were demonstrated to be less toxic, biodegradable, and effective in biocompatibility. Dendrimers possess a branched structure that can be easily modified which makes them good carriers for many active drug molecules. Complexed dendrimers have been shown to induce antiangiogenic responses in cancer models *in vivo*. Lipid nanoparticles can cross the blood-brain barrier making them useful for diagnosis and therapy for brain tumors.

As mentioned before, various surface modifications can be achieved on different nanostructures and conventional anti-tumor chemical drugs can be loaded into different nanocarriers in order to improve the pharmacological efficacy to target cancerous cells. It is important that both, researchers and clinicians take into account these specific characteristics in an effort to study and select the best option in a clinical setting. An extended summary of the most relevant research is listed in Table 3.

4.3. Liposomes

Liposomes are phospholipid vesicles with a spherical shape and can be produced spontaneously by making a phospholipid dispersion in aqueous media. During this process liposomes results in a bilayer structure, in the inner layer, the hydrophobic part of phospholipids are aligned and can be loaded with low soluble water drugs, while the inner space of the vesicle can be filled with hydrophilic drugs [124]. The size of liposomes can vary from 20 nm to hundreds of nanometers in diameter, and the thickness of the bilayer is between 5 and 7 nm. Some authors classify them by the diameter and the number of bilayers formed in the structure, there can be small single layer liposomes whose diameter is smaller than 100 nm, large single layer liposomes with diameters higher than 100 nm, and using the thin hydration method multiple-layer liposomes are obtained with several concentric lipidic bilayers [125]. For the fabrication of liposomes, the most commonly used lipid components are phospholipids, phosphatidylcholine, phosphatidylglycerol, phosphatidic acid, phosphatidylethanolamine, phosphatidylserine, etc. And the fabrication techniques can be classified into passive loading techniques that involve liposomes being charged before or during their formation, and active loading techniques involving processes where liposomes are charged once they are formed [126]. Liposomes fabrication methods and representations are shown in Fig. 6.

Due to its amphipathic properties, size, biocompatibility and, their ability to encapsulate hydrophilic and lipophilic compounds, multiple techniques have been developed for the production of liposomes [127]. The conventional technique is named hydration method, which consists in dissolving the phospholipids in an organic solvent and proceeding to evaporate the solvent in argon or nitrogen atmosphere, when this step is finished, thin phospholipids layers are formed over a glass surface, finally an aqueous solution is added and the phospholipids layer absorb the solution and the liposomes are formed [128]. Another technique used to prepare liposomes is called the heating hydration method, which is similar to the one mentioned before but with changes in the hydration step, where substances like ethylene glycol, propylene glycol, or glycerol are added in the aqueous phase in concentrations close to 3% at a

Table 2
Recent relevant research of polymeric nanoparticles for respiratory therapy.

Materials	Disease	Drug	Fabrication method	Efficacy tests	Cytotoxicity tests	Reference
Curland	Tuberculosis	Rifampicin/levofloxacin	Nanoprecipitation, incubation loading	*In vitro* MIC test	MTT assay (RAW 264.7 macrophages, L929 fibroblast), viability >85% (100 mg/mL)	[7]
PLGA	Tuberculosis	Linezolid	Emulsification-solvent evaporation	*In vitro* MIC test	Non reported	[23]
Chitosan	Tuberculosis	Silver nanoparticles	Modified nanoprecipitation	*In vitro* MIC test	Colorimetric method with crystal violet, IC_{50} of 12.3 μg/mL (A549 cell), IC_{50} of 357.2 μg/mL (WI 38 cell)	[8]
PLGA	Tuberculosis	Amikacin/moxifloxacin	Emulsification-solvent evaporation	*In vitro* viability of M. Tuberculosis H37Ra	Non reported	[24]
Poly(glycerol adipate-*co*-ω-pentadecalactone)	COPD	miR-146a	Emulsification-solvent evaporation	*In vitro* gene expression test	MTT assay (A549 cells), viability 65% (1.25 mg/mL)	[25]
PLGA	Acute lung sepsis	Sparfloxacin/tacrolimus	Emulsification-solvent evaporation	*In vitro* antibacterial assay, *in vivo* ICR mice model	Cell counting kit-8 (HUVEC cells), cell viability >90% (200 μg/mL)	[26]
mPEG-PLGA copolymer	NSCLC	Platinum complexes of curcumin	Nanoprecipitation	*In vitro* MTT assay, *in vivo* tumor growth and metastasis inhibition (BALB/c mice)	MTT assay (A549 cells), cell viability >90% (100 mg/mL, for empty nanoparticles), IC_{50} < 5 μmol/L (loaded nanoparticles)	[27]
PLGA/polyethyleneimine	NSCLC	Resveratrol-cyclodextrin complex	Emulsification-solvent evaporation	*In vitro* clonogenic assay, scratch assay	MTT assay, IC_{50} <~5 μM (A549, H157, H460, H4006, H358), cell viability >90% (HEK-293 cells, at 15 μM)	[28]
PLA	Asthma, COPD	Budesonide/theophylline	Double emulsification-solvent evaporation	Non reported	MTT assay (16HBE14o- cells), cell viability 66% (5 mg/mL)	[29]
PLGA	NSCLC	Febuxostat	Nanoprecipitation	*In vitro* cell cycle analysis	MTT assay (A549 cells), IC_{50} 52.62 μg/mL	[30]
PLGA	MERS-CoV	MERS-CoV RBD antigens with cyclic diguanylate monophosphate	Double emulsification-solvent evaporation	*In vivo* immunogenic test	Non reported	[31]
PLGA	NSCLC	PTX	Emulsification-solvent evaporation	*In vivo* tumor growth inhibition (Fox Chase SCID Beige mice)	MTS assay (A549 cells), IC_{50} (22 nM)	[32]
poly(cyclohexane-1,4-diyl acetone dimethylene ketal)/PLGA	Lung cancer	Doxorubicin	Double emulsification-solvent evaporation	*In vivo* histopathological examination (BALB/c mouse)	MTT assay (A549 cells), cell viability 38.31%	[33]
DSPE-PEG/Miglyol® 812	Lung cancer	Cisplatin, doxorubicin	Emulsification-solvent evaporation	*In vivo* tumor growth inhibition (C57BL/6 mice)	MTT assay (A549 cells), cell viability ~30% (100 μM)	[34]
Methoxy PEG-b-PCL	Lung cancer	DTX/osthol	Thin-film hydration	*In vitro* clonogenic assay (A549 cells)	MTT assay (A549 cells), IC_{50} 2852 nM	[35]
Methoxy PEG-b-PLA	Lung cancer	Alpinumisoflavone	Thin-film hydration	Non reported	*In vivo* toxicity assay, survival 100%, body weight loss 0% (20 mg/kg)	[36]

Abbreviations in table: MIC = minimal inhibitory concentration, MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, MTS = 2-(4-sulfophenyl)-2H-tetrazolium, IC_{50} = half maximal inhibitory concentration, RAW 267.4 = mouse leukemic monocyte-macrophage cells, L929 = mouse fibroblast cells, A549 = adenocarcinomic human alveolar basal epithelial cells, HUVEC = human umbilical vein endothelial cells, H157 = human oral squamous carcinoma cells, H460 = non-small human lung carcinoma cells, H4006 = human lung epithelial adenocarcinoma cells, H358 = human caucasian bronchoalveolar carcinoma cells, HEK-293 = immortalized human embryonic kidney cells, 16HBE14o- = human bronchial epithelial cells.

variable temperature that can reach up to 120 °C depending on the compounds added [129]. There is a liposome preparation technique based on a bruising change in the pH in which the phospholipids are dilute, causing the liposome to assemble and create a pH-sensitive liposome, this method is called the curvature tuning method [130] these liposomes have the advantage of being able to deliver not only drugs, but genes inside the cell by the endocytic pathway, being able to be used in therapies for lung cancer [131]. A single-step and fast method to produce liposomes is the spray-drying method, this technique is simple, the lipids are dissolved in an organic solvent with another compound to protect the phospholipids and then turned into liposomes in the spray-dryer, this method is also suitable for large-scale production and is effective for placing active compounds within liposomes [132].

Liposomes have been studied for the treatment of acute pulmonary inflammation by targeting the endothelium with antioxidant-loaded liposomes [133], also studied for the treatment of pulmonary infections loading liposomes with antibiotics [134–136], and pulmonary arterial hypertension treatment [137]. Some of the modifications purposed for the liposomes drug delivery are the combination with superparamagnetic nanoparticles to increase their targeting capacity, in the Nahar et al. [138] work the aim was to modify liposomes with starch-coated magnetic nanoparticles to reduce the systemic effects of pulmonary hypertension by keeping the inhaled liposomes in the respiratory tract by applying a magnetic field; also modification in the liposome surface with substances such as PVA can enhance the cellular targeting of the particles increasing its retention in the pulmonary tissue for peptide treatment in pulmonary diseases [139,140]; and modifying the surface of the liposomes to increase its stability and loading capacity [141].

Parvathaneni et al. [51], made liposomes of cholesterol and 1, 2-dipalmitoyl-*sn*-glycerol-3-phosphocholine by the thin-film hydration method loaded with pirfenidone to treat NSCLC, obtaining a reduction in cancerous cells of almost 10% more with liposomes loaded with pirfenidone (37.9%) than with just pirfenidone (28.4%) by itself; the major limitation in this study was the low load efficiency of pirfenidone into the liposomes due to its low solubility in water, however a strategy to improve the loading can be to change the conditions in the process of fabrication of the liposomes, like using a different pH as a gradient to

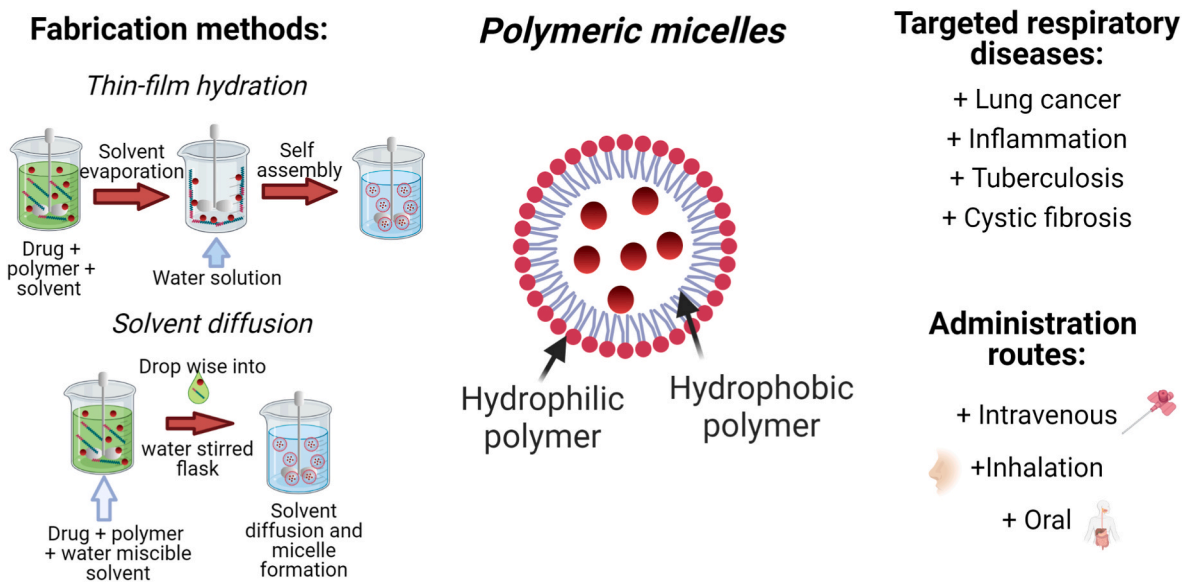

Fig. 5. Common fabrication methods, focusing diseases and administration routes of polymeric micelles in the treatment of respiratory diseases.

Table 3
Recent relevant research of micelles for respiratory therapy.

Materials	Disease	Drug	Fabrication method	Efficacy tests	Cytotoxicity tests	Reference
Chitosan	Tuberculosis	Rifampicin/ pyrazinamide	Dialysis	*In vitro* MIC test	MTT assay, negligible cytotoxicity (VERO cells), high toxicity (TPH-1 cells)	[6]
Inulin-vitamin E	Tuberculosis	Rifampicin	Dialysis	*In vitro* MIC test	MTT assay (human alveolar macrophages), viability 63% (2 mg/mL)	[37]
Chitosan-graft-poly (caprolactone)/(ferulic acid)	Tuberculosis	Rifampicin	Dialysis	*In vitro* inhibition test	Hemocytometer with trypan blue exclusion (A549 cells), IC_{50} of ~60 μg/mL*	[38]
α-tocopheryl succinate-PEG	Lung cancer	PTX	Thin-film hydration	*In vitro* MTT assay	MTT assay (A549 cells), IC_{50} ~1.5 μg/mL*	[39]
Poly (vinyl caprolactam)-poly (vinyl acetate)-PEG	Tuberculosis	Rifampicin	Solvent-diffusion	*In vitro* MIC test	CellTiter 96® (RAW 264.7), cell viability >85% (100 μg/mL)	[40]
Pluronic® 123/Pluronic® F127	Lung inflammation	Budesonide	Thin-film hydration	*In vivo* inflammation model (male Wistar rat)	Non reported	[41]
PEG-PLA/Pluronic® P105	Lung cancer	PTX	Thin-film hydration	*In vivo* tumor growth inhibition (BALB/c nude mice)	MTT assay (A549 cells), IC_{50} ~87.09 ng/mL	[42]
Soluplus®/d-α-tocopherol acid polyethylene glycol 1000 succinate)/ dequalinium	Lung cancer	Hinokiflavone	Thin-film hydration	*In vivo* tumor growth inhibition (BALB/c nude mice)	Cell counting kit-8 (A549 cells), IC_{50} 7.81 μg/mL	[43]
Cholesterol-conjugated PAMAM	Acute lung injury	Resveratrol/heme oxygenase-1 gene	Emulsification-solvent evaporation	*In vivo* lipopolysaccharide induce acute lung injury model (BALB/c nude mice)	MTT assay (L2 cells), cell viability >80% (15 μg/mL)	[44]

Abbreviations in table: MIC = minimum inhibitory concentration, IC_{50} = half maximal inhibitory concentration, MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, VERO = african green monkey kidney epithelial cells, TPH-1 = human leukemia monocytic cells, A549 = adenocarcinomic human alveolar basal epithelial cells, RAW 264.7 = mouse leukemic monocyte-macrophage cells, * = value read from a graph.

improve the drug loading. An extended summary of the most relevant research is listed in Table 4.

4.4. Lipid-based nanoparticles (LBNPs)

In this classification, we are considering both types of lipid nanoparticles, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). SLNs are formed from room temperature solid lipids, while NLCs combine room temperature solid lipids and oils enhancing the loading capacity in comparison to SLNs [142]. SLNs have a spherical shape and the diameter of the particle rounds between 10 and 1000 nm, and the core is stabilized by using surfactants allowing SNLs to solubilize lipophilic drugs [143]. As Sánchez-López et al. [144] mention the most used fabrication methods for lipid-based nanoparticles (LBNPs) are high shear homogenization and ultrasound, high pressure with hot and cold homogenization, solvent emulsification, and evaporation, and the microemulsion technique. Between most used ingredients for LBNPs fabrication reported are glyceryl monostearate, glyceryl palmitostearate, cetyl palmitate, and glyceryl behenate as solid lipids; medium-chain triglycerides and oleic acid as liquid lipids; and the surfactant Poloxamer 188 and Tween® 80 [145]. Lipid-based nanoparticles fabrication methods and representations are shown in Fig. 7.

Recently NLCs were tested by Ref. [55] to treat cystic fibrosis with lumacaftor and ivacaftor-loaded NLCs via inhalation with promising results. In lung infections NLCs have been modified with mannose to increase the targeting capacity in TB therapy [146], while Pastor et al.

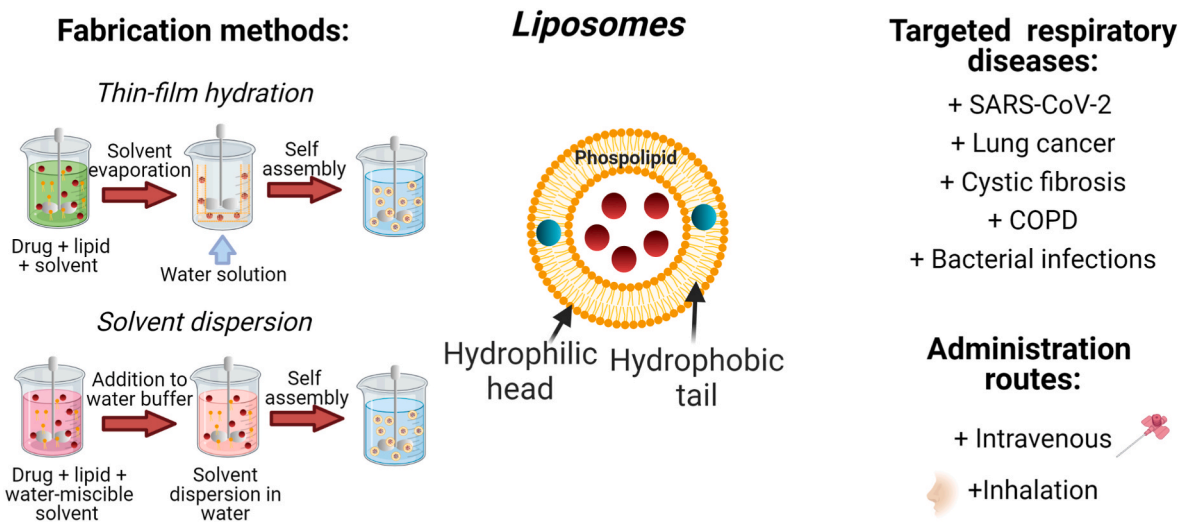

Fig. 6. Common fabrication methods, focusing diseases and administration routes of liposomes in the treatment of respiratory diseases.

Table 4
Recent relevant research of liposomes for respiratory therapy.

Materials	Disease	Drug	Fabrication method	Efficacy tests	Cytotoxicity tests	Reference
Small Unilamellar Liposomes, Pluronic® F127- surface modified liposomes and PEG 2000 PE-surface modified liposomes	Lung inflammation	Glucocorticoid beclomethasone dipropionate	Micelle-to-vesicle transition	Non reported	MTT assay (H441 cells), cell viability >80%* (20 mg/mL)	[45]
Folate-conjugated cholesteryl hemisuccinate	NSCLC	Doxycycline/DTX	Thin-film hydration	*In vivo* tumor growth inhibition (BALB/c nude mice)	MTT assay (A549 cells), IC_{50} 0.02398 μM	[46]
cholesterol/3-maleimidobenzoic acid N-succinimidyl ester/phosphatidylcholine	SARS-CoV-2	Nimbolide	Thin-film hydration	*In vivo* histopathological and ELISA tests (male C57BL/6 mice)	MTT assay (RAW 264.7 cells/BEAS-2B cells), cell viability >90%* (0.5 μg/mL)	[47]
Dipalmitoylphosphatidylcholine/ cholesterol	SARS-CoV-2	Hydroxychloroquine	Non reported	Non reported	Non reported	[48]
Phosphatidyl choline	SARS-CoV-2	Lactoferrin	Non reported	*In vitro* protein labeling assay (HaCaT cells)	Non reported	[49]
Soybean lecithin/cholesterol	Lung cancer	Curcumin	Thin-film hydration	*In vivo* histopathological and histochemistry analysis (male Sprague-Dawley rats)	Cell counting kit-8, cell viability ~6.28% (A549 cells, 100 μmol/L), cell viability >70%* (BEAS-2B cells, 100 μmol/L)	[50]
1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine/cholesterol	NSCLC	Pirfenidone	Thin-film hydration	*In vitro* scratch assay (A549 cells) and clonogenic assay (A549 cells, H4006 cells)	MTT assay, IC_{50} ~0.2 mg/mL (A549 cells), IC_{50} ~0.34 mg/mL (H4006 cells), IC_{50} ~0.24 mg/mL (H157 cells), IC_{50} ~0.15 mg/mL (H460 cells)	[51]
dipalmitoylphosphatidylcholine/ cholesterol	Refractory nontuberculous mycobacterial lung disease	Amikacin	Non reported	Clinical trial (NCT02344004)	Non reported	[52]
Phosphatidylcholine/cholesterol	Lung cancer	DTX	Thin-film hydration	Non reported	MTT assay (A549 cells), IC_{50} ~3.51 nM	[53]
1,2-Dioleoyl-*sn*-glycero-3-phosphocholine/n-(succinimidyloxy-glutaryl)-L-α-phosphatidylethanolamine, dioleoyl/monophosphoryl lipid A	SARS-CoV-2	SARS-CoV-2 receptor-binding domain	Thin-film hydration	*In vivo* vaccination study (BALB/c nude mice)	Non reported	[54]

Abbreviations in table: MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, IC_{50} = half maximal inhibitory concentration, HaCaT = human immortalized keratinocyte cells, H441 = human lung adenocarcinoma cells, A549 = adenocarcinomic human alveolar basal epithelial cells, RAW 264.7 = mouse leukemic monocyte-macrophage cells, BEAS-2B = human lung bronchial epithelial cells, H4006 = human lung epithelial adenocarcinoma cells, H157 = human oral squamous carcinoma cells, H460 = non-small human lung carcinoma cells, * = value read from a graph.

[147] loaded NLCs with colistimethate for the treatment of multi-resistant *Pseudomonas aeruginosa* infection through inhalation route; also the exploration of combining SLNs loaded with selenium nanoparticles and ciprofloxacin can result in enhanced antibacterial activity against *P. aeruginosa* preventing chronic infection [69]. Additionally, NLCs and SLNs have been tested to treat lung hypertension by loading sildenafil to this nanostructure made of precirol, beeswax, or stearic acid as solid matrix and oleic acid for NLCs, having good entrapment

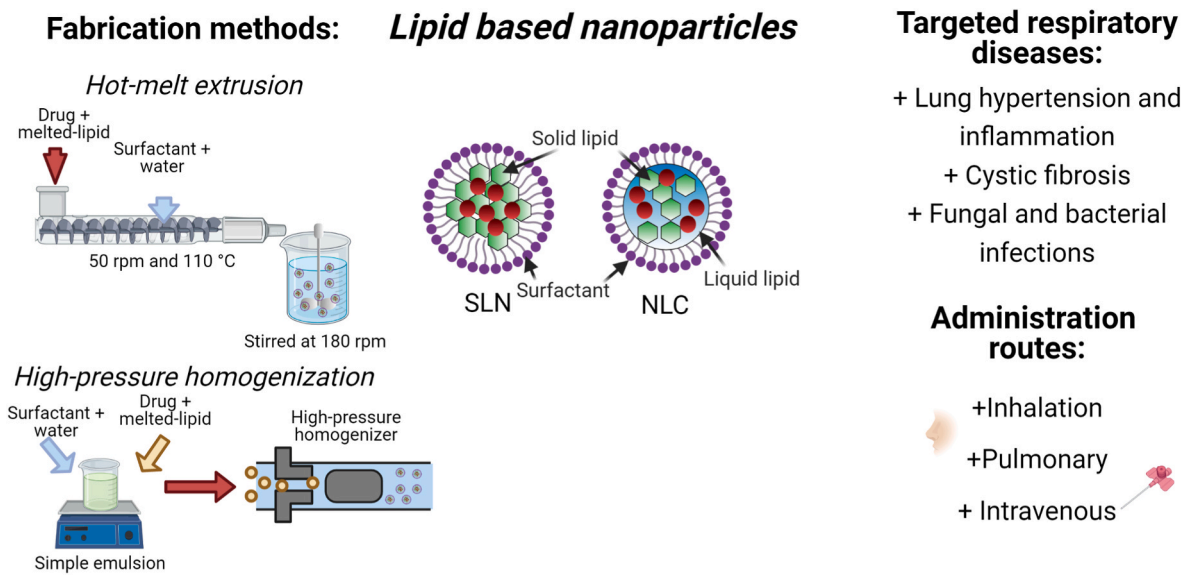

Fig. 7. Common fabrication methods, focusing diseases and administration routes of lipid based nanoparticles in the treatment of respiratory diseases.

efficiency (~95%) and prolonged release in the experiments [58]. In cancer gene therapy the exploration of surface-modified NLCs covering the nanoparticles with transferrin to target lung cancer cells has been successfully reported [148]. To successfully deposit nanoparticles in the deep lung area through inhalation, solid lipid nanoparticles often require to be submitted to further processes that can modify their structure so the original performance can be altered. The method of thin-film freeze drying (TFFD) method can be used to prepare SLNs dried powders that can enhance lung deposition with minimal SLNs structure modification, as in the work done by Wang et al. [56] where siRNA-loaded SLNs were submitted to TFFD, and then *in vitro* tested for lung deposition and siRNA function before and after TFFD, showing

Table 5
Recent relevant research of lipid based nanoparticles for respiratory therapy.

Materials	Disease	Drug	Fabrication method	Efficacy tests	Cytotoxicity tests	Reference
Precirol® ATO 5/squalene	Cystic fibrosis	Lumacaftor/ivacaftor	Hot emulsion-solvent evaporation	*In vivo* magnetic resonance imaging and computed tomography (Cftrtm1Unc Tg (FABPCFTR)1Jaw/J homozygote/homozygote bi-transgenic mice)	Non reported	[55]
Lecithin/cholesterol/stearoyl hydrazone PEG	Lung inflammation	TNF-α siRNA/1,2-dioleoyl-3-trimethylammonium-propane	Nanoprecipitation	*In vitro* cell transfection ELISA (J774A.1 cells)	Non reported	[56]
Oleic acid/Precirol® ATO 5	Bacterial lung infection	Ciprofloxacin	Hot-melt dispersion	*In vivo* histopathological analysis (male mice *Mus musculus*)	Non reported	[57]
Precirol® ATO 5/stearic acid or beeswax/oleic acid	Lung hypertension	Sildenafil	Hot emulsion-solvent evaporation	*In vivo* histopathological analysis (male Sprague-Dawley rats)	MTT assay (A549 cells), IC_{50} 0.348–1.02 mg/mL	[58]
Oleic acid/Precirol® ATO 5	Pulmonary aspergillosis	Itraconazole	Hot-melt extrusion	Non reported	Crystal violet assay (A549 cells), cell viability >90%* (0.5 μg/mL)	[59]
Cetyl palmitate	Lung cancer	Lumefantrine/nano calcium phosphate	Hot emulsion-solvent evaporation	*In vivo* tumor growth inhibition (BALB/c nude mice)	Non reported	[60]
Cholesteryl acetate/ cholesteryl palmitate/ cholesteryl butyrate/ Tripalmitin/Ascorbyl palmitate/2-phenylethanol/ polyoxyethylene (40) stearate	Bacterial lung infection	1,1′-(dodecane-1,12-diyl)-bis-(9-amino-1,2,3,4-tetrahydroacridinium) chloride/oligonucleotides	Hot emulsion-solvent evaporation	*In vitro* MIC test (*E. coli*)	MTT assay, IC_{50} ~130.2 μg/mL (Caco-2 cells), IC_{50} ~29.6 μg/mL (Calu-3 cells)	[61]
Palmityl palmitate	Tuberculosis	Isoniazid	Hot emulsion-solvent evaporation	*In vivo* antibiotic test (Wistar rats)	Cell counting kit-8, cell viability >90* (A549 cells), cell viability >90% (RAW 264.7 cells)	[9]

Abbreviations in table: TNF-α = tumor necrosis factor alpha, sIRNA = small interfering RNA, MIC = minimun inhibitory concentration, IC_{50} = half maximal inhibitory concentration, MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, J774A.1 = mouse BALB/c monocyte macrophage cells, A549 = adenocarcinomic human alveolar basal epithelial cells, Caco-2 = human colon adenocarcinoma cells, Calu-3 = human lung adenocarcinoma epithelial cells, RAW 264.7 = mouse leukemic monocyte-macrophage cells.

enhanced deposition and good siRNA function for TFFD treated SLNs. An extended summary of the most relevant research is listed in Table 5.

4.5. Dendrimers

Dendrimers are synthetic macromolecules with characteristics like high branching points, 3D shape, and globular structure at the nanoscale size. They have a characteristic structure containing three principal stages: a core consisting of a single atom or molecule; then from the core emanate some branches, formed from repeated units that are connected by at least one branch connection, this creates radial concentric layers called "generations'', and there are various terminal functional groups usually are located at the surface of the dendrimers, and they determine the properties of the structure [149]. The most representative characteristic of dendrimers is their tree-like structure resulting from the branch connections. In size, dendrimers are small structures that vary from 1 to 12 nm as the number of generations increases from 1 to 10 [150]. For drug delivery dendrimers some polymers proposed are polyamidoamine (PAMAM), poly(propylene imine), poly-L-lysine, melamine, poly(ether hydroxylamine), poly(esteramine), and polyglycerol. Dendrimers' fabrication methods and representations are shown in Fig. 8.

Dendrimer fabrication two approaches are followed; the divergent method consists in the coupling of monomeric molecules that have reactive and protective groups forming a generation, and further removing the protective groups to allow branching and form new generations; and the convergent method consists in forming surfaces by coupling monomers and advancing inward the structure [151]. The convergent technique starts with the synthesis of a wedge-like oligo--branched section named dendron which has a unique active functional group that works as a union deck to the other dendrons, several dendrons join to a core to form the dendrimer by interacting with the functional group. The convergent synthesis also provides full control in the structure of the dendrimers, byproducts or free molecules can be easily removed by their molecular weights, however, is more expensive than the divergent method of synthesis. The divergent method is generally cheaper than the convergent method and allows a quick increment in the mass of the dendrimer in each layer generated of the dendrimer, the almost unique disadvantage of this method can be related to the little errors that may happen in the formation of the branches in massive dendrimers production, however, this method is preferred for large-scale dendrimer synthesis [152]. In comparison with the other types of nanoparticles mentioned in this work, dendrimers are low studied in the treatment of respiratory diseases through respiratory routes, this can be a result of the cytotoxicity of these types of particles derived from their different charges in the surface of those structures which can make them highly reactive. To overcome this limitation some studies to modify the surface of the dendrimers with biocompatible polymers have been made, finding an increased performance in cell bioavailability studies and better trespassing through the pulmonary barriers such as the epithelium [153,154], and also analyzing the interaction with different surface modified dendrimers and the pulmonary surfactant layer which plays a critical role in the lungs functionality [155]. Even so, the exploration has been made of dendrimers for various pulmonary diseases, exploring the treatment of asthma by loading dendrimers with beclometasone dipropionate and studying the possibility of nebulizing the loaded dendrimers [156], and systemic delivery of proteins and peptides through the pulmonary route [157]. Also, surface-modified dendrimers have been studied in gene therapy with promising results *in vitro* experiments [158]. Kandeel et al. [62] used cationic and anionic dendrimers with hydroxyl, carboxyl, and succinamic acid terminated PAMAMs as terminals groups to prevent the plaque formation of MERS-CoV, obtaining a diminution of about 40% with anionic dendrimers. Tyssen et al. [159] prepared lysine dendrimers by the divergent method with a core of benzhydryl amide of (L)-lysine; which has been previously used to inhibit the activity of the HIV-1 virus; this same procedure was used by Paull et al. [64] to inhibit the replication of SARS-CoV-2 *in vitro*. An extended summary of the most relevant research is listed in Table 6.

4.6. Exosomes

Exosomes are extracellular vesicles derived from cell membranes formed of a phospholipid bilayer, and they vary in size from 40 nm to 120 nm [160]. Exosomes are produced naturally from various types of cells (if not all), and play a major role in cell communication by transporting different types of molecules such as proteins, lipids, and genetic material from a donor cell to a receptor cell [161]. Due to their natural origin in animal cells, exosomes have low or non-toxicity and low clearance rates, additionally they are naturally provided with biomarkers to promote the interaction of exosomes with the receptor cell membrane or medium signaling to promote cellular uptake giving them

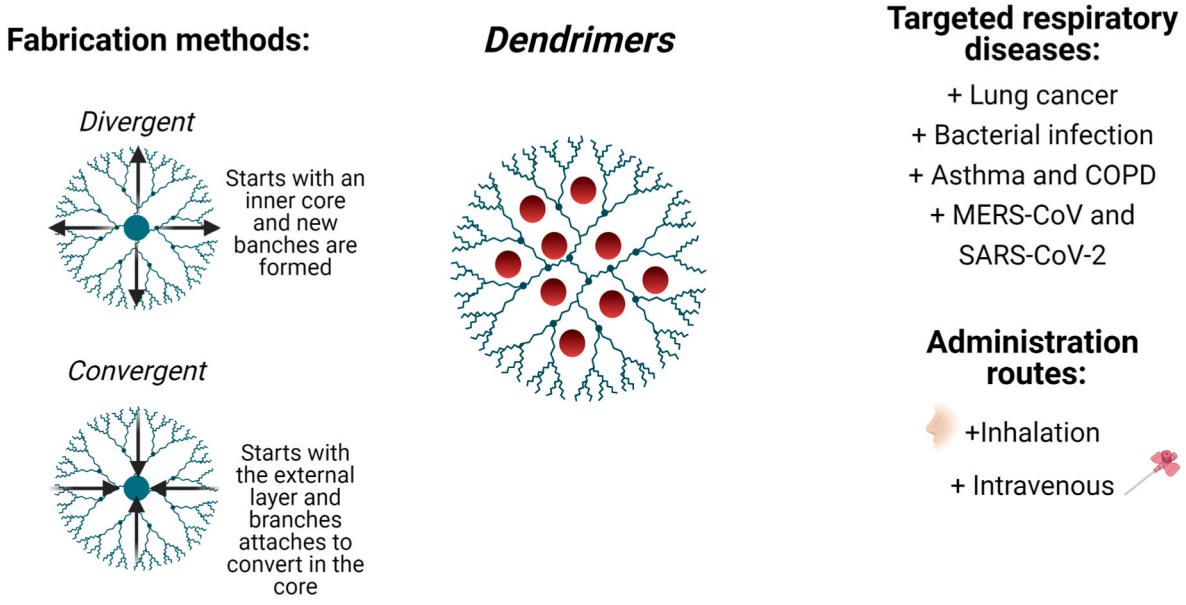

Fig. 8. Common fabrication methods, focusing on diseases and administration routes of dendrimers in the treatment of respiratory diseases.

Table 6
Recent relevant research of dendrimers for respiratory therapy.

Materials	Disease	Drug	Fabrication method	Efficacy tests	Cytotoxicity tests	References
PAMAM	MERS-CoV	Sodium carboxylate, hydroxyl, or succinamic acid in anionic dendrimers and cationic dendrimers	Divergent reaction	*In vitro* plaque formation assay (VERO cells)	Non reported	[62]
PAMAM	Lung inflammation	TNF-α siRNA	Divergent reaction	*In vivo* cytometric bead array - mouse inflammation kit (CD-1 mice)	MTT assay (RAW264.7 cells), IC_{50} 3750 nM	[63]
Generation-four lysine dendrimer with a polyanionic surface charge	SARS-CoV-2	Astodrimer sodium (SPL7013)	Non reported	*In vitro* antiviral efficacy test	IC_{50} 2.93 mg/mL (VERO E6 cells)	[64]
PAMAM	Lung cancer	Doxorubicin	Divergent reaction	*In vivo* lung metastasis model (male C57BL/6 mice)	MTT assay (B16–F10 cells), IC_{50} 5.85 μM	[65]
PAMAM	NSCLC	HuR siRNA/*cis*-diamine platinum	Non reported	*In vitro*	Trypan blue exclusion assay, cell viability 50% (100 nM, H1299 cells), cell viability 38% (100 nM, A549 cells), cell viability 82% (100 nM, MRC9 cells)	[66]
POxylated generation4 polyurea dendrimers	Pulmonary arterial hypertension	Sildenafil	Supercritical-assisted polymerization	Non reported	MTS assay (A549 cells), cell viability >95%* (250 nM)	[67]
Phosphorus dendrimers of generation 3	Lung inflammation	TNF-α siRNA	Divergent reaction	*In vivo* lipopolysaccharide induce acute lung injury model (female CD-1 mice)	MTT assay (RAW 264.7 cells), IC_{50} 41 μg/mL	[68]
Zwitterionic gadolinium(III)-PAMAM	Lung cancer	Gold nanoparticles	Divergent reaction/ Michael addition reaction	*In vivo* lung metastasis model (mice)	Cell counting kit-8 (B16 cells), cell viability >90% (400 μM)	[69]

Abbreviations in table: TNF-α = tumor necrosis factor alpha, siRNA = small interfering RNA, HuR = human antigen R, MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, MTS = 2-(4-sulfophenyl)-2H-tetrazolium, IC_{50} = half maximal inhibitory concentration, VERO = african green monkey kidney epithelial cells, RAW 264.7 = mouse leukemic monocyte-macrophage cells, VERO E6 = african green monkey kidney epithelial cells clone E6, B16–F10 = mouse skin melanoma cells, H1299 = non-small human lung carcinoma cells, A549 = adenocarcinomic human alveolar basal epithelial cells, MRC9 = Medical Research Council cell strain-9.

great targeting properties [162]. Before mentioned properties make exosomes especially interesting for drug delivery, for this purpose they can be loaded with drugs or genetic material following two major types of techniques; passive loading which broadly consists in exposing the donor cell to a therapeutic or diagnostic molecule while the exosome is formed so the drug is loaded during exosomes formation, or the active loading were drugs are loaded once the exosomes are formed, they are submitted to a physical process to promote the drug diffusion into the exosome [163]. But once the exosomes were passively charged, or even before an active charge method, exosomes must be isolated from the rest of the components present in the medium. To achieve this multiple techniques of isolation exist, such as differential centrifugation, filtration, chromatography, and polymer precipitation [164]. Exosomes fabrication methods and schematic representation is shown in Fig. 9.

As mentioned before, to obtain exosomes necessary for drug delivery purposes, two main processes are needed, the isolation of exosomes from

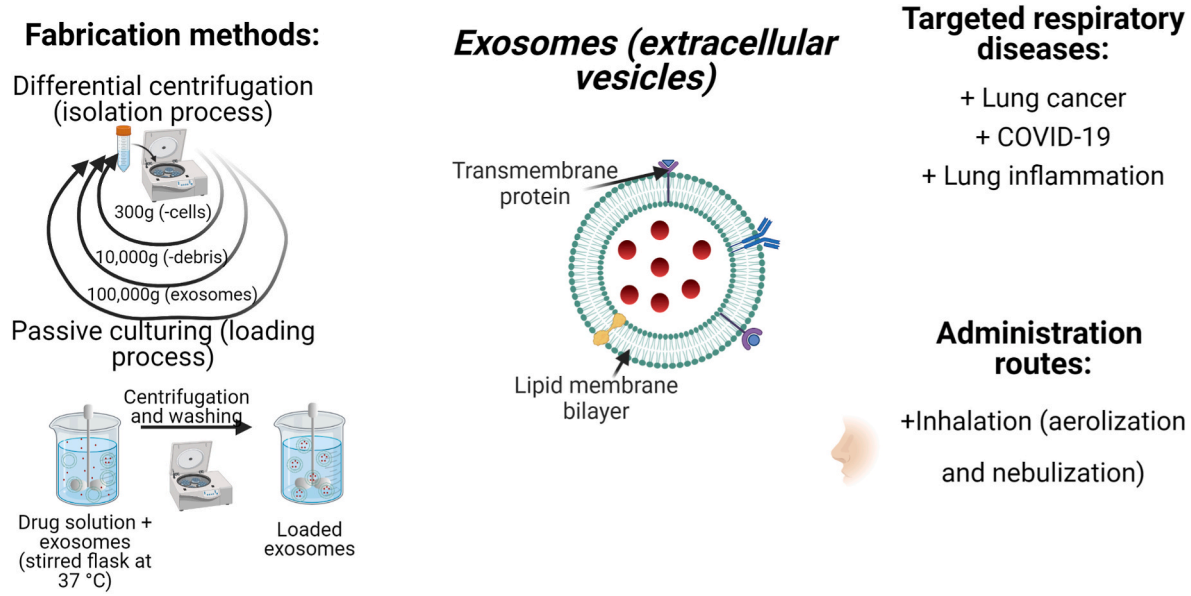

Fig. 9. Common fabrication methods, focusing on diseases and administration routes of exosomes in the treatment of respiratory diseases.

the cellular medium that contains them, and the loading of the exosomes with the therapeutic agent. The most common method used for exosome isolation is differential ultracentrifugation, this method consists in applying various steps of centrifugation and further ultracentrifugation, on every step different components are discarded such as cells, dead cells, bigger exosomes, and cell debris [165]. But also for lung therapy, exosomes have been isolated by polymer precipitation method, this method consists in adding water-excluding polymers that can trap exosomes and other low soluble molecules to form clusters. The increase of size in the cluster can allow the precipitation of exosomes by something the solution to a normal centrifugation process, reducing the cost of isolation. Even though the advantages of polymer precipitation techniques, lower recovery and more impurities can be found when compared with the ultracentrifugation standard [166,167].

Recently, exosome studies in respiratory therapy were focused on lung cancer therapy. Srivastava et al. [168] studied the possibility of combining the exosomes with doxorubicin-gold nanoparticles obtained from a process of linking the drug with the gold nanoparticles using a pH-sensitive linker, this combination of nanoparticles allows obtaining a retarded release and more bioavailability and reduced toxicity (both *in vitro*) when compared to the free drug and doxorubicin-gold nanoparticles alone. Instead of modifying the load of exosomes, some studies have focused on modifying the surface of exosomes to enhance their targeting abilities. This can be reached by the genetic modification of exosome donor cells to express certain biomarkers in the exosome's surface [169]. Also, exosomes derived from edible plants have been proposed for COVID-19 treatment, an *in silico* study carried out by Kalarikkal & Sundaram [170] modulate the blocking of COVID-19 RNA replication by the coupling of ginger and grapefruit derived exosomes loaded with miRNA, even though the promising results, further *in vivo* studies still needed to validate the specificity of miRNA and discard the possible toxicity of the treatment. An extended summary of the most relevant research is listed in Table 7.

5. Clinical translation and market status of nanostructured drug-loaded nanocarriers

To develop functional DDS systems that can be applied in the clinical stage is necessary to complete a series of steps. These steps can be resumed in three major stages: (1) preclinical trials, (2) clinical trials, and (3) industrial production. Every step is crucial for the proper development of DDS that can be commercially available. Each step has certain components of interest that are discussed in further subsections.

5.1. Preclinical trials

Preclinical development can be defined as those studies where a new drug delivery platform is proposed, in this step the nanostructured is experimentally fabricated, followed by physicochemical characterization, to then finally be tested *in vitro* and/or *in vivo*. In this step, the selection of the drug, type of nanostructure and the materials are the basic concepts. In spite of this, there are a wide number of variables that need to be measured and considered.

The selection of the fabrication method highly influences the physicochemical and biological properties but is also important to consider the reproducibility of the method and its industrial translation, complex fabrication methods can result in impossible or highly expensive industrial translation, which does not ensure a cost-effective product [171,172]. In fact, common physicochemical properties measured in the literature are size and its distribution, morphology, the surface charge, and releasing profile [173]. Even though this might not be sufficient to properly characterize the nanostructures, e.g. just a few studies consider the studies of stability under different storage conditions at long periods, which is a critical factor for market translation.

On the other hand, the biological properties of DDS are mainly focused on the short-term toxicity of the nanostructure. Even when short-term toxicity is a crucial step of platform screening, in most cases a single dose will not be sufficient, thus more exhaustive studies analyzing the effect of long-term toxicity and interactions of the proposed nanostructures are needed. Some studies have reported the presence of adverse effects as pseudo allergic reactions and immunosuppression after long-term exposure [174,175] in animal models, which can also be an important criterion for screening of new DDS. Also, biodistribution plays an essential step, it allows us to know where the nanostructures will tend to accumulate and how fast the organism will take to eliminate DDS, this information can be an important tool for predicting its clinical behavior [176]. These situations can be condensed into a critical issue, due to the relative novelty of this new type of drug platform, nanostructures in therapy are still not properly regulated, it is necessary to establish proper and rigorous methods that allow an adequate characterization of the nanostructures.

Table 7
Recent relevant research of exosomes for respiratory therapy.

Materials	Disease	Drug	Fabrication method	Efficacy tests	Cytotoxicity tests	References
Medical Research Council cell strain-9 (MRC9)/human non-small cell lung carcinoma cell line (H1299) derived exosomes	NSCLC	Doxorubicin-conjugated gold nanoparticles	Differential centrifugation/ passive loading	*In vitro* mitochondrial perturbation assay (H1299, A549 cells)	Trypan blue exclusion assay, cell viability 58.8% (H1299 cells), cell viability 46.6% (A549 cells), cell viability 59.3% (MRC9 cells)	[168]
tLyp-1-lamp2b plasmids transfected HEK293T cells derived exosomes	NSCLC	Cy3-siRNA	Differential centrifugation/ electroporation loading	*In vitro* transfection efficiency test (A549 cells)	Non reported	[169]
Milk from pasture-fed Holstein and Jersey cows derived exosomes	NSCLC	Celastrol	Differential centrifugation/ passive loading	*In vivo* tumor growth inhibition assay (female athymic nude (nu/nu) mice)	MTT assay, IC_{50} 0.9 μM (A549 cells), IC_{50} 0.6 μM (H1299 cells)	[180]
Adipose-derived stem cells derived exosomes	Oxidative stress caused by $PM_{2.5}$ exposure	Nrf2 overexpressed exosomes	Differential centrifugation	*In vivo* $PM_{2.5}$ exposure test (Sprague-Dawley rats)	Non reported	[181]
Ginger/grapefruit derived exosomes	SARS-CoV-2	miRNA	Polymeric precipitation	*In silico*	Non reported	[170]

Abbreviations in table: HEK293T = immortalized human embryonic kidney cells, $PM_{2.5}$ = fine particulate matter 2.5 or less microns, IC_{50} = half maximal inhibitory concentration, Cy3-siRNA = Cy™3 dye–labeled synthetic small interfering RNA, Nrf2 = nuclear factor erythroid 2–related factor 2, MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, H1299 = non-small human lung carcinoma cells, A549 = adenocarcinomic human alveolar basal epithelial cells, MRC9 = Medical Research Council cell strain-9.

5.2. Clinical trials

In Table 8 there is a summary of different clinical studies of nanostructures being tested for the treatment of different respiratory diseases. The data was recovered from ClinicalTrials.gov, the type of nanostructure, drug, disease, and phase presented from studies started on January 1st of 2018 and after. Liposomes were the principal nanostructures being at a clinical trial, which has been reported by other previous studies, due to their biocompatibility and easy fabrication methods. Liposomes are followed by exosomes, where mesenchymal stem cells-derived exosomes are being studied to treat inflammation and promote regeneration produced in diseases like new COVID-19 or bacterial pulmonary infections [177,178]. Just a few studies on LBNPs were found, one focused on lung cancer treatment, but more interesting is the studies of LBNPs in the fabrication of new vaccines for COVID-19 prevention, currently administered Moderna and Pfizer vaccines use lipid nanoparticles to encapsulate the genetic material [179], what may suggest the trends in the use of LBNPs in gene therapy.

A special mention in the clinical trial NCT04490200 was chitosan nanoparticles are used to prime semi-facial respirators in order to increase the efficacy of masks in air filtering against viruses and bacteria, especially for the SARS-CoV-2 protection of medical staff in hospitals. So, we can highlight that nanoparticles can be used not only for treating pulmonary diseases, but also to prevent them by improving medical equipment. Nonetheless, polymeric nanostructures (nanoparticles, micelles, and dendrimers) still present a poor clinical translation in terms of therapeutic development. This can be argued in the sense of lack of clarity of the fate of nanoparticles after cellular uptake, the majority of the studies only focus on the short time effects, but when the degradation cycles at physiological conditions are prolonged (months, and even years); effects of DDS accumulation in tissues and organs require more studies.

Moreover, it can be easily seen that nanostructures with more biological-like (or biological-derived) compositions (liposomes, exosomes, and LBNPs) have a stronger tendency to be used in clinics.

Respiratory care devices are being extensively used for treatment, diagnosis monitoring, and controlling respiratory disorders. Moreover, according to the Respiratory Care Devices Market, the smart inhalers market size was $28.62 million in 2019 and is projected to reach $445.40 million by 2027 [182]. In the US and the EU, there are different commercially available devices to treat respiratory disorders such as metered-dose inhalers (MDI), dry powder inhalers (DPI), a pressurized metered-dose inhalers (pMDI), and nebulizers, in Table 9 we show examples of inhalable products available on the market until 2020.

6. Discussion

The main objective of this review is to understand the tendencies, advances, and limitations of research for novel DDS therapy in pulmonary diseases. As can be seen in Table 1 leading technology, polymeric nanostructures (nanoparticles and micelles) are leading the chart with the biggest number of publications, this can be explained due to the boom in biocompatible polymers research. In addition, polymeric nanoparticles compared to other nanostructures have the advantage of versatility which includes the addition of functional groups, control over polymer chain length, stimulus response modifications, and co-polymer formulation [183,184]. Moreover, a variety of new polymers are found every year. Research focused on polymeric nanoparticles has enabled precise tuning of pharmaceutical properties (bioavailability, biocompatibility, degradability, etc.) [185]. Which points out the importance of more research in new polymeric DDS. From same Table 1 in second place, the lipidic structures such as liposomes and LBNPs, these types of structures have a good balance between pharmaceutical properties and ease of production; yet, liposomes are the most studied lipidic DDS, many authors have attributed their success due to their similarity to the cellular membrane in composition, allowing them to have good biocompatibility and cellular uptake [186]. In third place from Table 1 is placed the exosomes technology, these relatively new DDS are naturally produced by cells, and this could give them the highest biocompatibility and biodegradability among the reviewed structures. On the other hand, the loading and isolation techniques could be limiting its scalability and translation to the markets [187]; all things considered, it can be expected an increase in the number of publications in exosome research for next years. Dendrimers are the structure with the least number of publications in the period reviewed, despite their fabricacion is well-known, and there are many companies that produces dendrimers at large scale, their role in DDS can be limited by their biocompatibility; terminal groups in dendrimers can be highly reactive, this make them cytotoxic structures by their own, which can be desired in the treatment of cancer, but a critical concern in many other diseases. Nonetheless, this can be a

Table 8
Nanostructures in clinical studies from 2018 to the present.

Nanostructure	Drug	Disease	Phase	Administration Route	ClinicalTrials.gv Identifier
Polymeric nanoparticles	N/A	SARS-CoV-2	N/A	N/A	NCT04490200
Micelle	PTX	NSCLC	Phase 1	Intravenous	NCT04778839
Liposome	Irinotecan	Small cell lung cancer	Phase 2	Intravenous	NCT04727853
Liposome	Amphotericin B	Invasive pulmonary aspergillosis	Phase 1	Inhalation (nebulization)	NCT04267497
Liposome	Amikacin	Mycobacterium fnfections, nontuberculous	Phase 3	Inhalation (nebulization)	NCT04677569
Liposome	Cyclosporine A	Bronchiolitis obliterans and lung transplant rejection	Phase 3	Inhalation (nebulization)	NCT03657342
Liposome	Amphotericin B	Pulmonary mucormycosis	Phase 2	Intravenous	NCT04502381
Liposome	Lactoferrin	SARS-CoV-2	Phase 2/ Phase 3	Oral and intranasal	NCT04475120
Lipid based nanoparticles	Quaratusugene ozeplasmid	Lung cancer	Phase 1/ Phase 2	Intravenous	NCT04486833
Lipid based nanoparticles	SARS-CoV-2 wild-type S-spike mRNA	SARS-CoV-2	Phase 1	Intramuscular	NCT04566276
Exosomes	Human adipose-derived mesenchymal progenitor cell exosomes	Drug resistant lung infection (gram negative bacilli)	Phase 1/ Phase 2	Inhalation (aerosol)	NCT04544215
Exosomes	Allogenic adipose mesenchymal stem cells derived exosomes	SARS-CoV-2	Phase 1	Inhalation	NCT04276987
Exosomes	SARS-CoV–2 specific T cell derived exosomes	SARS-CoV-2	Phase 1	Inhalation (aerosol)	NCT04389385

Source: https://clinicaltrials.gov/

Table 9
Commercially available nanostructures for pulmonary disorders.

Brand name	Manufacturer	Active substance	Administration route/Device	Indication (s)
TOBI® PODHALER™	Novartis	Tobramycin	Oral inhalation use/DPI	Cystic fibrosis patients with *Pseudomonas aeruginosa.*
ASMANEX TWISTHALER	Merck	Mometasone furoate	Oral inhalation use/DPI	Asthma as prophylactic therapy
DULERA®	Merck	Mometasone furoate and Formoterol fumarate dihydrate	Pressurized inhalation suspension/pMDI	Asthma
SEREVENT DISKUS	GlaxoSmithKline	Salmeterol xinafoate	Oral inhalation use/DPI	Asthma
SPIRIVA® RESPIMAT®	Boehringer Ingelheim	Tiotropium	Inhalation solution/Nebulizer	COPD, asthma
Ventolin®Respirator Solution	GlaxoSmithKline	Salbutamol sulfate	Solution/Nebulizer	Bronchospasm
Tilade®	Sanofi	Nedocromil sodium	Pressurized inhalation suspension/pMDI	Asthma
BricanylÒ Turbohaler®	AstraZeneca	Terbutaline sulfate	Oral inhalation/DPI	Bronchodilator
CAYSTON®	Gilead	Aztreonam	Inhalation solution/Nebulizer	Cystic fibrosis
RELENZA	GlaxoSmithKline	Zanamivir	Oral inhalation use/DPI	Influenza
VIRAZOLE®	Valeant	Ribavirin	Inhalation Solution/Nebulizer	Respiratory tract infections due to RSV

pMDI = Pressurized Metered Dose Inhaler, DPI = dry-powder inhaler, RSV = respiratory syncytial virus.

desirable feature giving dendrimers a great capacity to be surface-modified and increase its biocompatibilty and safety [188].

In summary on disease applications, it can be noticed that most of the research in DDS for lung therapy is focused on cancer treatment, this can be attributed to the high numbers of deaths by lung and bronchial cancer and the constant increase of patients with cancer every year [189]. Also, tuberculosis has gained interest due to the constant increment in drug resistant cases. This disease has been challenging to treat during many years, this gave the opportunity to DDS research to focus on new treatments for tuberculosis [190]. In contrast, many other relevant lung diseases such as cystic fibrosis, asthma, COPD, and, caused by pathogens (with exception of SARS-CoV-2 due to the urgency of the current pandemic) are studied [19]. Therefore, there is an important need for more research beyond lung cancer, even tuberculosis still being poorly studied in comparison with lung cancer therapy.

7. Challenges

Given the complexity of developing new therapies based on nanotechnology it is important to find novel strategies to improve treatments based on DDS. Multiple properties of nanostructures can be enhanced such as stability, accumulation, and penetration into target tissues and the ability to sort biological barriers [191,192]. Inhalation route for DDS delivery presents a significantly lower clearance rate for nanoparticles when compared with intravenous or oral administration routes, this is because particles administered by inhalation avoids the first-pass metabolism, resulting in increased bioavailability of the drug and extended circulation time of the nanoparticles [193]. Despite the advantages, different biological barriers must be circumvented to successfully deliver the drug into the desired action site, which can be a specific lung section or specific cell type. For example, particle deposition (which is not strictly a biological barrier, but is in fact a physical barrier) is one of the main challenges to solve in order to successfully deposit the DDS. The aerodynamic properties of particles will define the site where most of them will deposit, thus, the aerodynamic properties must be modified depending on the respiratory tract section of interest for the therapeutic (commonly for respiratory diseases, the deep lung region is the relevant site for therapy).

Size-dependent deposition of inhaled particles represents an important challenge for nanoparticle delivery systems. The most important parameter for lung deposition of inhaled particles is the particle size, characterized by the aerodynamic diameter. Previous studies have shown that nanoparticles (in the range of 1–5 μm) show a high degree of deep lung deposition while smaller particles can be exhaled and bigger particles will tend to deposit in the outer regions of the respiratory tract [194]. Therefore, the design of DDS for lung delivery is usually a constant trade-off between the excellent aerodynamic properties of particles at the microscale, against the increased cellular uptake and bioavailability of nanoscale particles. Some studies have explored different techniques to overcome this challenge without sacrificing any of the properties mentioned before, for example bulking loaded nanoparticles using bulking agents such as mannitol and trehalose can increase the aerodynamic diameter of particles to reach an appropriate scale for optimal deposition and keeping the size of the original nanoparticles [195]. Microencapsulation, as the name implies, looks for generating nanoparticles for drug delivery and then being encapsulated inside microparticles of some easily degradable material that once microparticles reach the lung tissue it begins to release the nanoparticles [196,197]. In any case, bulking or microencapsulation, care must be taken to avoid the modification of the original properties of nanoparticles while are submitted to the increase of size process, and any extra material used must be biocompatible, non-toxic, and should allow a rapid release of nanoparticles once the lung deposition is done [195].

As mentioned in Chapter 3, the reticuloendothelial system represents another challenge to take into account when designing nanostructures. The presence of pulmonary macrophages can reduce the effectiveness of DDS therapeutics [198]. When DDS are administered into the respiratory system, usually the objective is to reach the lung epithelium tissue either to deliver the drug into epithelial cells or to reach the circulatory system for systemic delivery, however, the macrophage uptake can result in an important decrease of bioavailability [199]. In this sense, the modification of DDS must be done to avoid macrophages and other defense cells to enhance the effectiveness of drugs. Also, the presence of mucus in the respiratory tract has an important role in lung drug delivery. Nanoparticles with a size greater than 200 nm will be trapped by the glycoprotein network that conforms to the mucus [200]. In addition to particle size, the surface charge of the DDS will define if the particles interact with the mucus barrier, in this sense, it has been shown that neutral DDS has better diffusion into the mucus layer [201].

In both cases, reduction of macrophage uptake and mucus permeation, the use of polyethylene glycol (PEG), also known as polyethylene oxide (PEO), for coating of DDS is the most common method to avoid (or reduce) the macrophage uptake in nanoparticles. Polyethylene glycol (PEG) is a linear polyether with the molecular formula HO–$(CH_2–CH_2–O)_n$-H, one of the most interesting characteristics of this polymer is the hydrophilicity that gives it the capability to have reduced protein binding, and therefore, increased bioavailability, biocompatibility, and slow clearance rate in the organism [202]. Due to the previously mentioned properties of the PEG, this polymer has been used to coat different pharmaceutical agents such as proteins, enzymes, bioactive molecules, and DDS, in order to increase its biocompatibility and reduce their clearance rate; this process is known as PEGylation and has

gained a lot of interest since the 1970s to the date. Nonetheless, it has been reported the production of specific PEG antibodies in both, animal models and patients. The specific binding of antibodies to PEGylated DDS produces undesired effects like the reduction of the effectivity of the treatment, due to the increase of PEGylated DDS clearance (known as accelerated blood clearance effect), and the onset of hypersensitivity reactions that can provoke from severe to deadly pseudo-allergic reactions [203,204]. Multiple studies have focused on the understanding of immunogenic response to PEGylated DDS, in general terms, factors associated with the PEG characteristics are: the length (molecular weight), the terminal group (that can be hydroxy, amino, methoxy, butoxy, tert-butoxy), the density of the PEG coating; nevertheless, factors associated with the DDS such as the size, hydrophilicity, and immunogenicity (of the DDS, and the loaded drug itself) that can trigger different immunogenic responses [204,205]. In summary, despite the knowledge about the PEGylated immunogenic response, it is not appropriate to fully discard the use of PEG as a coating for DDS, or to provide optimal configuration for PEG to successfully coat specific DDS. More studies will be required to give a final conclusion to this issue. Hence, continuous attempts have been made to find a coat that can provide DDS enhanced circulation times and satisfactory bioavailability. New alternatives to PEG have appeared, among the alternatives available are: the use of hydrophilic polypeptide chains of alanine, glutamic acid, glycine, proline, serine and theorine; other hydrophilic polymers like poly(glycerols), poly(oxazolines), poly(hydroxypropyl methacrylate), poly(vinyl)pyrrolidone, poly(N,N-dimethyl acrylamide), among others; and zwitterioninc polymers such as poly(carboxybetaine) and poly(sulfobetaine) [205–207].

8. Conclusions and future directions

Respiratory diseases are a major burden in terms of morbidity and mortality throughout the world. Undeniably, nanotechnology-enabled drug delivery systems in clinical practice represent a critical tool to improve patient survival and quality of life. Nanotechnology has gained great interest in the past decades for drug delivery, the potential benefits of the use of nanostructures are the possibility of developing targeted therapies for certain diseases. Nanostructures exhibit multiple advantages such as biocompatibility, low toxicity, sustained and controlled release, capacity for targeting, multifunctionality, and high aqueous solubility. The present review discusses the most representative work in the field of drug delivery nanostructures for respiratory diseases treatment. We outline strategies for engineering nanoparticles to improve several crucial properties to make them more efficient to treat respiratory diseases. Additionally, it was pointed out the importance of finding new materials to make nanostructures less toxic, to show sustained and controlled release in the respiratory tract, and to improve capacity for targeting and sorting biological/physical barriers.

To date, there are some DDS commercially available, most of them correspond to liposome nanostructures, probably because of the reduced toxicity and enhanced bioavailability of this type of nanostructures when compared with others. Therefore, the development of new materials or finding new formulations from known materials that potentially overcome the challenges of the DDS is still significant in this field of research. However, it also requires more effort in understanding the interaction between complex biological systems with nanoscale systems giving the tools for proper design of new DDS platforms which can reach the clinical application that ultimately will benefit patients.

Credit author statement

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Declaration of competing interest

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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