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Review article

Nanotherapeutics in the treatment of acute respiratory distress syndrome

Pragya Prasanna [a,1], Shweta Rathee [b,1], Arun Upadhyay [c], Sulakshana Sulakshana [d,*]

[a] Department of Biotechnology, National Institute of Pharmaceutical Education and Research (NIPER), Hajipur, Bihar 844102, India
[b] Department of Food Science and Technology, National Institute of Food Technology Entrepreneurship and Management, Sonipat, Haryana 131028, India
[c] Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA
[d] Department of Anesthesiology and Critical Care, Sri Ram Murti Smarak Institute of Medical Sciences (SRMS-IMS), Bareilly, Uttar Pradesh 243202, India

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is a form of oxygenation failure primarily characterized by rapid inflammation resulting from a direct pulmonary or indirect systemic insult. ARDS has been a major cause of death in the recent COVID-19 outbreak wherein asymptomatic respiratory tract infection progresses to ARDS from pneumonia have emphasized the need for a reliable therapy for the disease. The disease has a high mortality rate of approximately 30–50%. Despite the high mortality rate, a dearth of effective pharmacotherapy exists that demands extensive research in this area. The complex ARDS pathophysiology which remains to be understood completely and the multifactorial etiology of the disease has led to the poor diagnosis, impeded drug-delivery to the deeper pulmonary tissues, and delayed treatment of the ARDS patients. Besides, critically ill patients are unable to tolerate the off-target side effects. The vast domain of nanobiotechnology presents several drug delivery systems offering numerous benefits such as targeted delivery, prolonged drug release, and uniform drug-distribution. The present review presents a brief insight into the ARDS pathophysiology and summarizes conventional pharmacotherapies available to date. Furthermore, the review provides an updated report of major developments in the nanomedicinal approaches for the treatment of ARDS. We also discuss different nanoformulations studied extensively in the ARDS preclinical models along with underlining the advantages as well as challenges that need to be addressed in the future.

1. Introduction

Acute respiratory distress syndrome (ARDS), first recognized in 1967, is a clinical syndrome linked with oxygenation failure due to pulmonary or systemic insult [1,2]. It is the most common reason for respiratory failure in critically ill patients, commonly characterized by sepsis, alveolar damage (both epithelial and endothelial), high permeability, noncardiogenic pulmonary edema, and hypoxemia [3]. According to Berlin's definition, the disease is an acute form of diffused lung injury prevalent in patients with worsening respiratory symptoms that cannot be entirely explained by heart function or fluid accumulation with pulmonary edema and onset of hypoxemia [4,5]. The mortality rate ranges from 35 to 50%, depending on the severity of ARDS, and the quality of life also remains very poor in the survivors [6]. Disease management strategies may primarily include respiratory support through mechanical ventilation, nutritional supplementation, and limited fluid intake. Unfortunately, no effective pharmacological treatments or approved medicine for ARDS exist [7].

The recent pandemic caused by a novel coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV-2), known as Coronavirus disease -2019 (COVID-19), is a fatal condition that has led to millions of deaths worldwide, mainly in patients suffering from other medical conditions (referred as comorbidity) [8]. ARDS is one of the primary manifestations and the foremost cause of death in COVID-19 patients [9,10]. Previously, ARDS has caused high mortality during the widespread SARS infections and the Spanish influenza pandemic [11,12].

Abbreviations: ARDS, Acute respiratory distress syndrome; AT-I, Alveolar type I cells; AT-II, Alveolar type II cells; CO, Carbon monoxide; CO2, Carbon dioxide; COVID-19, Coronavirus disease 2019; GLP-1, Glucagon-like peptide 1; GNP, Gold nanoparticle; ICAM-1, Intercellular Adhesion Molecule-1; IL-6, Interleukin-6; MSCs, Mesenchymal stem cell; NPs, Nanoparticles; PLGA, Poly (lactic-*co*-glycolic acid); SARS-CoV2, Severe acute respiratory syndrome coronavirus 2; TLR-4, Toll-like receptor-4; TNF-α, Tumor necrosis factor-alpha; PAMAM, Poly-amidoamine; PLL, Poly-L-lysine; PPI, Polypropylenimine.

* Corresponding author at: Department of Anaesthesiology and Critical Care, SRMS-IMS Bareilly, Bareilly 243202, Uttar Pradesh, India.
E-mail address: dr.sulakshanatripathi@gmail.com (S. Sulakshana).

[1] Authors contributed equally.

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The outbreak of COVID-19, wherein asymptomatic respiratory tract infection progresses to severe pneumonia to ARDS, has once again emphasized the urgent requirement for a reliable therapy for the disease.

Presently, the mortality rate and severity of ARDS is high and we do not have any reliable medical therapy available for the disease [13]. The current ARDS management strategies are merely limited to supportive care like lung-protective ventilation, extracorporeal membrane oxygenation, conservative fluid management, etc. [221,222]. The diagnosis of this syndrome relies on the appearance of clinical symptoms that could lead to delayed identification or many a time an incorrect evaluation of the actual clinical burden [14]. The extent of lung injury cannot be measured directly, and there is a lack of specific diagnostic tools or biomarkers for ARDS. The development of several symptoms is required to ascertain the extent of the disease's severity which ultimately results in delayed therapeutic support and patient care. Despite numerous randomized controlled trials for ARDS, a handful of successful outcomes reflect the futility of the interventions [15]. The insufficiency of pharmacotherapies could be partially attributed to the impeded drug-delivery to the damaged alveoli, insufficient accumulation of drugs in the lungs, low circulation half-life, and inability to cross physiological barriers (mucus and alveolar fluid) for systemic delivery [16–18].

In the past few decades, the ability of nano-based drug candidates to deliver bioactive compounds selectively to the pulmonary tissues in recommended concentrations and with considerable safety has motivated the scientific community [16,19–21]. The application of nano-drug-delivery systems holds the potential to improve the available clinical intervention strategies of ARDS by mechanisms, such as facilitating the stimulus-induced biodegradation of drugs in the body, allowing nano-encapsulated drugs to escape the endocytic degradation pathway, ensuring sustained drug delivery, and promoting the delivery of active ingredients to the specific targets [22,23]. In this review, we have provided a brief introduction of the disease, its pathophysiology, and available pharmacotherapies along with discussing the challenges associated with it. Subsequently, we highlighted the significance of nanotherapeutics as an effective, potent, and next-generation strategy for the treatment of ARDS.

2. The pathophysiology of ARDS

ARDS pathophysiology is a complex phenomenon mainly characterized by the fluid accumulation in the alveoli and injury in the lungs as a result of pathogenic or physiological insult and subsequent immune response [24]. Presumably, disruption of the alveolar barrier is considered as the major cause of lung injury and acute inflammation experienced in ARDS [26]. Under normal conditions, various osmotic and hydrostatic forces counterbalance each other and maintain the tight junctions between alveolar epithelium allowing a very small amount of fluid to be carried by the pulmonary tissues into the interstitium [27]. Besides, the selectivity to fluids and solutes is established by the coordination of several endothelial cells, adherens, and tight junctions. With the help of Na^+/K^+-ATPase pumps and Na^+ channels, the alveolar epithelium maintains the fluid concentrations in the air space [28]. Additionally, flat alveolar type I (AT-I) and cuboidal type II (AT-II) cells of the alveolar epithelium helps in the exchange of carbon dioxide (CO_2) with oxygen across the alveolar-capillary units. These epithelial cells restrict the small-sized solutes from entering the epithelium, thereby allowing CO_2 and oxygen to pass through it readily [28,29].

ARDS pathogenesis can be classified into three broad phases: exudative, proliferative, and fibrotic [29]. The exudative phase of ARDS, in particular, is characterized by excessive inflammation with endothelial and epithelial permeability and alveolar damage due to fluid accumulation in the interstitium [30]. Studies suggest that providing an effective intervention in the exudative phase may prevent the onset of the later fibrotic phase and increase the chances of a patient's survival [31]. However, the inability to prevent the exudative phase triggers the proliferative phase characterized by an amplified inflammatory response and activation of procoagulant pathways. The advent of the proliferative case may in few cases lead to the restoration of the alveolar architecture but in the majority of the cases, this phase is followed by the onset of the fibrotic phase, wherein significant fibrosis of the lungs results in the decreased gas exchange, reduction of pulmonary compliance, and increased hospital mortality [32,33].

An injury to the lung either caused due to extrinsic factors like infection, trauma, or some intrinsic factors, leads to the altered fluid balance causing an accumulation of fluids in the interstitial spaces giving rise to edema [34]. Concurrently, the trigger of a range of inflammatory chain reactions in the body results in the activated inflammatory response that aids in fluid reabsorption and pathogen clearance to some extent [35–37]. However, excessive inflammation may damage alveolar tissues by altering the composition of endothelial and epithelial cells, eosinophilic depositions, cell hyperplasia, and interstitial fibrosis. Excessive immunological response leading to the release of chemokines, cytokines, leucocyte proteases, neutrophils, and reactive oxygen species causes alveolar injury [38,39]. The damage to alveolar cells contributes to the enhanced endothelial and epithelial permeability across the lungs leading to the accumulation of protein-rich alveolar fluid [34,40]. Moreover, dysregulated inflammation of vascular tissues often activates innate immune pathways which cause acute lung injury by neutrophils mediated disruption of junction proteins that may progress to a greater degree of hypoxemia, causing ARDS [41,42].

In healthy lungs, VE-cadherin and E-cadherin proteins are required to maintain the endothelial barrier and lung epithelium integrity in lung microvessels respectively [43]. The alveolar injury leads to increased concentrations of vascular endothelial growth factor, thrombin, tumor necrosis factor-α (TNF-α), and leucocyte signals which leads to the destabilization of the vascular endothelial cadherin bonds. This dysregulated inflammatory response and increased epithelial and endothelial permeability result in an increased accumulation of intra-alveolar fluid and impaired oxygenation. Furthermore, the recruitment of neutrophils, macrophages, and effector T-cells inside the alveoli propagates the injury to other parts of the lungs [44–46]. In Fig. 1, a diagrammatic representation of all the major events and changes occurring in the alveoli that leads to the onset of ARDS has been shown.

3. Pharmacotherapies for ARDS: current status

The majority of pharmacotherapies studied so far in the prevention and treatment of ARDS are merely supportive and do not ensure complete relief. It includes corticosteroids, aspirin, nitric oxide (NO), β-2-agonists, statins, vitamin C, and carbon monoxide (CO) [47,48]. The impairment of alveolar fluid clearance commonly observed in ARDS is addressed through fluid management strategies [49–51]. Another promising therapy for ARDS relies on steroids like dexamethasone which could suppress pulmonary inflammation in ARDS by inhibiting the production of proinflammatory cytokines [52,53]. Similarly, ulinastatin, an anti-inflammatory agent is considered another reliable therapy for ARDS [54]. The antioxidant property of Vitamin C has also been found to decrease mortality and delay the development of ARDS [55]. Anticoagulants like heparin are also considered as an effective therapy for ARDS. It helps in the restoration of the impaired coagulation system [56,57]. Excessive inflammatory responses and tissue damage can be prevented with the help of an active process referred to as the resolution of inflammation. Molecules such as lipoxins, protectins, and resolvins are known to possess pro-resolution effects [58–61]. These pro-resolving mediators are significantly considered for managing pulmonary diseases, including ARDS and COVID-19 [62].

Optimal delivery of drugs to the lungs in the form of aerosols inhaled through the airway is an effective strategy to deliver drugs in the distal lung regions minimizing acute oxidative lung damage and side-effects. Therefore, several inhalation therapies have also been successfully tested, such as inhalation of CO and NO in low doses by patients with

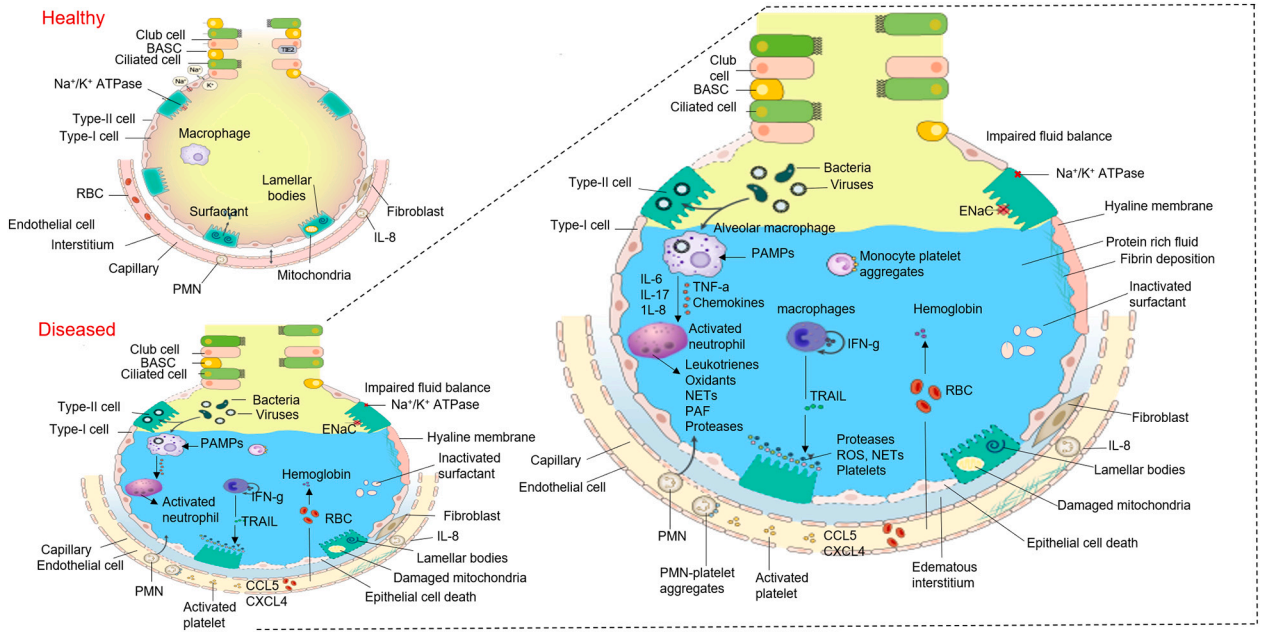

Fig. 1. A comparative illustration of physiological changes in the alveoli under healthy and diseased ARDS conditions has been shown: The alveolar epithelium consists of a layer of Alveolar type I cells (ATI) cells that allow gas exchange to occur, and Alveolar type II cells (ATII) cells are present to produce surfactant enabling lung expansion with low surface tension. Both ATI and ATII cells can be used to transport fluid and ions from the alveolus. The epithelial cells of alveoli are interconnected with tight junctions, which act as a barrier and controls fluid movement. Under normal conditions, water and few solutes do not cross the epithelial layer; thus, the alveolar lumen is free of fluid. Under diseased conditions, fluid accumulates in the alveolar lumen.

Table 1
List of common therapeutic agents and their mechanisms of action in ARDS.

Agent	Molecular target	Mechanism of action	Model	Reference
17-AAG	HSP90	Attenuates LPS-induced inflammation in lungs by NF-κβ mediated inflammatory response	HLMVECs	[184]
TPCA-1	IKK-2	Inhibit the production of TNF-α, IL-6, and IL-8 in LPS treated monocytes	Mice	[13]
Oleic acid	Elastases	Inhibit superoxide anion and elastases in activated neutrophils	Mice	[171]
Chelerythrine	NF-κB	Attenuation of inflammation	RAW264.7 cells; Mice	[185]
Oridonin	Anti-inflammatory	Weakens release of pro-inflammatory cytokines by inhibiting expression of TLR4/MyD88 and phosphorylation of NF-κB p65 in lung tissues	RAW264.7 cells; Mice	[186]
Glucosteroids	Anti-inflammatory, anti-fibrotic	Improves organ function score, lung injury score, and oxygenation	Human	[187]
Dilmapimod	p38MAPK	Reduces inflammation	Human	[188]
GSK1995057	TNF receptor-1	Attenuated inflammation due to selective inhibition of TNFR1 signaling inhibiting cytokine and neutrophil adhesion molecule expression	Human	[189]
Solnatide (AP301)	Na+ channels (Type II cells)	Enhances alveolar fluid clearance by activating epithelial sodium channels	Human	[190]
Citrulline	–	Increase nitric oxide synthase levels	Human	[191]
Angiotensin II	Angiotensin II	Improves oxygenation, while reducing cellular infiltrate and fibrosis	Rats	[192–194]
Anticoagulants	–	Decreases coagulation and inflammation without altering systemic coagulation	Rats	[56,57,195]
ALT-836	Tissue factor	Anti-TF antibody	Human	[196]
Heparin	Tissue factor, plasminogen activator inhibitor-1, plasminogen	Anticoagulant	Rats	[57]
Streptokinase	Thrombolytic agent	Decreases PaCO2; Improves oxygenation and lung mechanics	Human	[197]
Elafin variant (GC/QQ-elafin)	Elafin	Increases protease resistance, Improved anti-inflammatory activity for pulmonary inflammation	Mice	[198]
Imatinib	Bronchoalveolar lavage protein, TNF-a	Attenuates inflammation and vascular leakage	Mice	[199]
Bevacizumab	Vascular endothelial growth factor	Suppresses vascular endothelial growth factor-induced high permeability pulmonary edema	Mice	[200]
Pirfenidone	NLRP3	Ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis	J774A.1, Mice	[201]
Tetracycline	Metalloproteinases, Elastase	Blocks multiple proteases and cytokines	Pigs	[202,203]
Dihydromyricetin	NLRP3	Alleviates Sepsis-Induced Acute Lung Injury	Mice	[204]
Lipoxin A4	Fas-ligand/tumor necrosis factor α	Inhibit fibroblast proliferation; type II cell wound repair	Alveolar type II cells	[205]
TRPV4 inhibitors	TRPV4	Alleviate macrophage activation and ventilator-induced lung injury	Mice	[206]
GW328267C	Adenosine A2A receptor	Improves lung function after acute lung injury	Rats	[207]
Haptoglobin	Heme-oxygenase-1	Lower alveolar macrophages	Mice	[208]
Melatonin Apocynin	NLRP3	Block histone-induced NLRP3 inflammasome activation	Mice	[209,210]

Abbreviations: HLMVECs, Human lung microvascular endothelial cells; NLRP3, NLR family pyrin domain containing 3.

ARDS. Inhalation of CO is well-tolerated and safe as it shows both antioxidant and anti-inflammatory activity [63]. Inhaled NO has also been shown to be well tolerated and effective in ARDS patients as it helps in the significant improvement of oxygenation [64]. In recent years, many studies have reported the potential benefits of these pharmacological agents in ARDS disease models. A summary of these pharmacotherapeutic agents having a promising therapeutic benefit in ARDS is presented in Table 1.

4. Mesenchymal stem cell (MSC) therapies

Cell-based therapies like bone marrow-derived multipotent mesenchymal stem cells (MSCs) have broad therapeutic applications in clinical conditions like sepsis and organ failures. MSCs are also being considered as a novel intravenous therapy for the early treatment of ARDS. The results of multiple studies have substantiated a significant reduction of lung inflammation and mortality in ARDS without causing much toxicity [65–67]. Both preclinical studies and clinical trials have shown MSCs as an exceptionally efficacious therapy in acute lung injuries as well as in ARDS [65–70]. The reasons lie in the capability of MSCs to differentiate into alveolar epithelial/endothelial cells restoring the epithelial permeability, reduced inflammation, and repair injured tissues [71–75]. Furthermore, human MSCs can restore alveolar epithelial fluid transport and normal fluid balance caused due to acute lung injury/ARDS [69]. They can be easily extracted from bone marrow, fat, amniotic membrane, etc. [73]. These self-renewing cells can differentiate in a multidirectional manner and suppress excessive inflammation by inhibiting pro-inflammatory factors, such as IL-6, TNF-α, etc.

MSCs are also known to have antioxidative benefits through their property of decoupling oxidative phosphorylation [77]. Studies suggest that MSCs promote clearance of fluid accumulated inside alveoli and increase the levels of fibroblast growth factor 10 and angiopoietin-1 [68,75,78] The release of angiopoietin-1 by MSCs restores the permeability of both endothelial and epithelial cells [68,75]. Moreover, MSCs produce different growth factors, such as, hepatocyte growth factor, keratinocyte growth factor, and vascular endothelial growth factor, which helps in the regeneration of type II alveolar epithelial cells [50,79,80]. Despite commendable advancement in the pace of clinical testing, crucial knowledge gaps must be reduced to enhance its therapeutic potential [71].

5. Nanotechnology-based drug delivery systems in ARDS

Though nanotechnology dates back to the 1950s, nanomedicine is a relatively new domain of interdisciplinary science established in the late nineties [82,83]. To date, only a handful of nano-modified drugs have been approved by the FDA [84]. Nanotechnology has offered several drug-delivery vehicles as a biocompatible and biodegradable carrier platform for water-insoluble drugs, peptides, etc. [85,86]. These delivery methods provide solutions to many crucial pharmacological challenges, like lower drug uptake, shorter half-life, poor pharmacokinetics, etc. [16,20,21]. Nanoscale particles possess unique physicochemical properties that can be used to improve the physical and biological properties of drugs in terms of solubility, selectivity, efficacy, pharmacokinetics, and toxicity [84,87]. It also helps overcome challenges like stability, bioavailability, and systemic distribution of the long-acting nanocarriers [88].

Though pulmonary nanomedicine is an under-explored domain, several nano-modified drugs have been studied that offer numerous advantages in the treatment of both chronic and acute lung diseases [89,90]. It presents a promising platform that bestows a plethora of drug-delivery vehicles with uniform distribution sustained drug-release in plasma and internalization throughout the alveoli [91]. Nanoparticles with a size <5 μm have been shown to exhibit higher lung deposition and enhance the dissolution of poorly water-soluble medicines [92]. Different types of NPs that have been fabricated and studied for pulmonary drug-delivery applications and ARDS have been depicted in Fig. 2. Drug-distribution to the deeper pulmonary tissues is a prerequisite in ARDS due to profound endothelial cell damage. The low resolution, rapid clearance, shorter half-life, and ineffective delivery of drugs to the target organs have limited the efficacy of pharmacotherapies.

In recent years, multiple drug-delivery systems have been developed and tested on ARDS experimental models to address the above-described limitations. To some extent, researchers have achieved success [89]. For

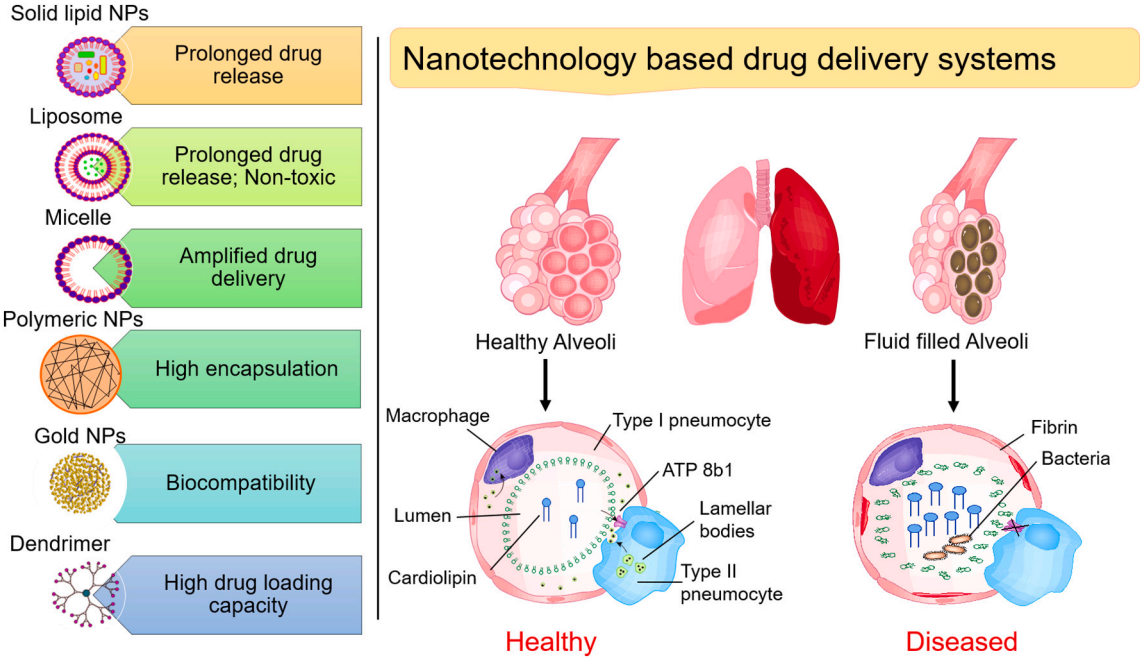

Fig. 2. Types of nanotechnology-based drug delivery systems targeting pulmonary tissues and explored especially in the context of ARDS along with their unique advantages have been shown. The cross-section of alveolar cells in both healthy and diseased conditions has been shown to indicate the differences that need to be considered while designing these nanoparticles.

instance, NPs facilitate sustained drug release of specific drugs in the systemic circulation, leading to reduced dosage frequency. Similarly, NPs decorated with specific ligands help target-specific drug-delivery which minimizes the undesirable interactions in the body and reduces the amount of drug intake thus, minimizing the side effects [94]. The nanoscale particles remain hyperactive affecting inflammatory and oxidative stress reactions due to the large surface area per unit mass of NPs [95–97]. The NPs-induced aggravated lung inflammation may be reflected through the increased oxidative stress and high expression levels of pro-inflammatory cytokines [98]. Under hyper-inflammatory conditions, NPs can readily cross epithelial and endothelial cell layers and gain entry into the blood circulation [99,100].

The coupling of nanostructured delivery systems with drugs and bioactive molecules allow uniform distribution and internalization of drugs in well-aerated alveoli and targeted drug-delivery, along with minimizing adverse drug reactions [101,102]. The drug delivery systems can be re-engineered to serve diverse clinical needs. For example, chemical modifications of NPs by hydrophilic agents can prolong its clearance by reducing its reticuloendothelial system-mediated opsonization [101,103]. Recently, a liposomal formulation of amikacin has reached the final stage of clinical trials for bronchiectasis, a condition of damaged bronchial tubes [105]. Researchers anticipate this development as a stepping stone towards the bright future of pulmonary nanomedicine [105]. An antibody-coated liposome-mediated approach has been shown to target pulmonary endothelium directly; thus, overcoming the pharmacological challenges of ARDS [106].

In a study, NPs comprising of simvastatin-loaded nanostructured lipid carriers conjugated with anti-ICAM-1 (intercellular adhesion molecule-1) provided several encouraging features in the treatment of acute lung injuries, such as increased drug uptake, optimistic histological improvements, and lower pulmonary TNF-α and IL-6 levels [107]. The study further showed that antibody-tagged nanocarriers could accumulate at very high levels in the lungs and can be effectively used to deliver NPs to the diseased endothelium as well [108,109]. The specificity of NPs to target diseased endothelium depends on their shape; for example, nanorods are more specific in targeting endothelial cells than nanospheres [111]. This correlation between the shape of NPs and the specificity of endothelial targeting can be used to target diseased endothelium in ARDS. In a study, rod-shaped NPs attached to the RBC surface through non-covalent interactions have been shown to increase the accumulation of NPs in the lungs [112]. A comprehensive list of such novel nanotherapeutics currently studied at the preclinical level in the ARDS models has been provided in Table 2. Moreover, few crucial classes of NPs explored in the ARDS models have been summarized in the following sections.

5.1. Polymeric NPs

Polymeric NPs are mainly composed of polymers such as poly (lactic-co-glycolic acid) (PLGA), gelatin, alginic acid, and chitosan. In general, these polymers are quickly metabolized inside the body and are considered safe and biodegradable [113–115].

Polymeric NPs are gaining popularity in pulmonary drug delivery due to several advantages such as better drug encapsulation capability, safeguarding drug moieties from degradation, sustained drug release, and prolonged shelf life [116–118]. Nanoparticles made up of biodegradable polymers are biocompatible and suitable for aerosolization, selective-targeting, the pre-determined release of the drug, and degradation within an acceptable period [119,120]. The surfaces of these NPs can be readily modified using specific ligands and receptors for targeted drug-delivery and avoid off-target side effects. [121]. PLGA-NPs modified by chitosan are effective tools to enhance drug delivery efficiency by exploiting the mucoadhesive properties of chitosan [122,123]. Chitosan nanoparticles are well known for promoting peptide absorption across mucosal surfaces of deeper lung tissues [124]. These NPs can be delivered directly to the deeper alveolar tissues optimizing lung therapy with efficient drug delivery [125]. Additionally, the incorporation of curcumin to chitosan NPs has shown an excellent anti-inflammatory effect [126,127].

5.2. Lipid-based nanocarriers

Lipid-based nanocarriers are another drug delivery system that is well-suited for delivering therapeutic agents to the pulmonary tissues. These drug delivery systems are comparatively less toxic and facilitate prolonged drug-release and drug deposition into the deeper tissues [128–130]. These nanocarriers may be classified into polymeric micelles, nanostructured lipid carriers (NLC), solid lipid nanoparticles (SLN), and liposomes. In the following subsections, we discussed different classes of lipid-based nanocarriers applied for pulmonary drug-delivery, especially in the ARDS models.

5.2.1. Polymeric nanomicelles

Polymeric micelles are amphiphilic sterically stable macromolecules usually spherical in nature [131]. These lipid-based nanoparticles of the size ranging from 10 to 100 nm are made up of polyvinyl pyrrolidone, polyethylene glycol, polyvinyl alcohol, polyglycerols [132]. The micelles can be further functionalized with antibodies or specific ligands for greater cell penetration, response to stimuli, such as pH, redox, light, heat, etc. Nanomicelles have been anticipated to treat inflammatory lung conditions, including ARDS. Formulation of a glucagon-like peptide-1 (GLP-1) in the form of micelles has been shown to prolong its bioactivity and half-life [133]. In general, peptide drugs have a very short half-life (sometimes only a few minutes) and are insoluble in an aqueous solution thereby, hindering drug distribution in the body [134]. Human GLP-1 is a superfamily of intestinal amphipathic peptides [135]. These peptides have been found to inhibit activation of NF-κB in cultured macrophages as well as in a murine model of ARDS [136]. However, the efficacy of GLP-1 is limited by its short half-life, which, if improved, could lead to a potential ARDS therapeutic strategy [137].

5.2.2. Solid lipid nanoparticles (SLNs)

SLNs are colloidal NPs capable of delivering therapeutic peptides, proteins, antigens, and drugs (both hydrophilic and lipophilic) to their specific targets [138,139]. They are more stable and tolerant in comparison to other lipid-based NPs, such as liposomes. For pulmonary application, maximum drug loading and sustained release of the bioactive molecules from lipid-containing matrix-based systems are considered the most suitable ones. The active ingredient is incorporated in the lipid core or deposited at the lipid core surface [140]. Several studies have shown that soybean oil, long-chain triglyceride, medium-chain triglyceride, and fish oil have an anti-inflammatory effect and pro-resolving influences on ARDS patients [141–143]. Solid lipid nanoparticles, a lipid-based nanoparticle encapsulating curcumin, have also been reported to decrease inflammation and cytokine expression [144].

5.2.3. Liposomes

Liposomes made up of surfactants, phospholipids, and cholesterol comprises an important drug delivery system, widely known for their sustained-release properties and non-toxic nature [145,146]. They are also used for pulmonary applications [147]. Interestingly, the first liposomal product Alveofact® was introduced for ARDS in 1999. Since then, liposomes have been extensively used for pulmonary drug-delivery [148–150]. Liposomes functionalized with groups, such as mannose, have been found to increase alveolar cell uptake, whereas attaching them with specific antibodies increases tissue targeting and local drug release in the lungs [151,152]. In several studies, liposomes have been shown to deliver drugs like amphotericin B and paclitaxel in pulmonary diseases [153,154]. The liposomal formulation of *N*-acetylcysteine has shown improved prophylactic efficacy against lipopolysaccharide-induced lung injuries in animal models displaying ARDS pathology

Table 2
Nanoparticle-based delivery systems with the proposed mechanism of action in ARDS.

Nanomedicine	Formulation components	Active ingredients	Size	Experimental model	Mechanism of action	Advantages	References
Polymeric NPs	PLGA	a-2,8 NANA	–	C57BL/6 mice, human ex vivo lung perfusion (EVLP) model	Upregulated IL-10 level	Targeting Siglec receptors under inflammatory conditions	[211]
	PLGA	YSA peptide (YSAYPDSVPMMS)	256 nm	HUVECs, Mice	Anti-inflammatory	Increased cellular uptake	[114]
	PLGA	EpoR cDNA	196 nm	Human type-1 alveolar epithelial cells, Sprague-Dawley rats	Upregulation of EpoR expression	Attenuated lung tissue damage	[212]
	PBA, PEG-Biotin	TPCA1	100 nm	HUVECs, Adult CD-1 mice	pH-responsive action	Improved endothelial targeting and uptake	[117]
	DAEPA	CFC	195 nm	Ex vivo rabbit lung model	Inhalable delivery of nanoparticles	Increased pulmonary delivery	[213]
Nanomicelles	PEG	GLP-1	15 nm	C57B6/DBA mice	Amplifies drug delivery to the lung	Prolonged bioactivity by preventing rapid peptide degradation in vivo	[133,137,214]
	GP-682	Lev	60 nm	BEAS-2B cells, Male KM mice	Enhanced cell membrane permeability and drug targeting	Improved efficacy	[215]
	PS-PEG	Surfactant	47 nm	C57/BL6 mice	Produce extremely low surface tension at high compression	Aqueous injectable dosage form	[216]
NLC	ICAM-NLC	Angiopoietin-1 simvastatin	228 nm	EAhy926, Male BALB/c mice	Up-regulated Ang-1, attenuation of pulmonary TNF-α and IL-6 levels	High cellular uptake	[107]
	ICAM-NLC	Dexamethasone	249 nm	EAhy926, male BALB/c mice	Attenuated pulmonary inflammation	Low cytotoxicity and enhanced cellular uptake	[109]
Lipid core nanocapsules	PEC, SMS, CTG	α-Bisabolol	160 nm	Male A/J mice	Reduction in pulmonary inflammation	An anti-inflammatory effect related to the inhibition of the MAPK pathway	[217]
Liposomes	DPC	N-Acetylcysteine (NAC)	200 nm	Male Sprague–Dawley rats	Lessening the effects of ROS and inflammation	Provide higher antioxidant delivery and retention of NAC in the lung	[155]
Nanovesicles	DPC-DOPE	Surfactants	300 nm	Swiss albino mice	Improved adsorption at low pH and lower surface tensions	Decreased alveolar protein leakage and superior airway patency	[119]
Gold NPs	Gold	FFFFFF	13 nm	THP-1 cells, ALI mice	Targeting TLR4 signaling in macrophages	Size-dependent control of endotoxin tolerance for treatment	[166,167]
	Gold	CLPFFD	13 nm	THP-1 cells, PBMC	Inhibits both TLR4-triggered NF-κB and IRF3 activation, and the secretion of a variety of proinflammatory cytokine	Amino-acid dependent attenuation	[218]
Dendrimers	PAMAM	SiRNA	153 ± 11 nm	RAW264.7, Female swiss CD-1 outbred mice	Enhanced in vitro silencing efficiency of TNF-α	Strong potential in the delivery of siRNA	[219]
	Phosphorus	SiRNA	120 nm	RAW264.7, CD-1 mice	Enhanced in vitro silencing efficiency of TNF-α	Strong potential in the delivery of siRNA	[169]
Miscellaneous	Glycyrrhizin	TLR-4/NF-κb	200 nm	RAW264.7 cells	Inhibition of the signaling pathway	Better anti-inflammatory activities	[48]
	Oleic acid	–	103 nm	Male C57BL/6 mice	Suppressed the superoxide anion and elastase produced by the stimulated neutrophils	Nanocarriers mitigated myeloperoxidase and cytokines more effectively as compared to Oleic acid solution	[171]
	Polystyrene	ICAM-1	200 nm	BALB/c mice	Reduced opsonization and RES clearance	Increased drug accumulation in the lungs	[112]
	Polystyrene	–	20 nm, 100 nm	Rat alveolar epithelial cell monolayers	PNP translocate primarily transcellular	High cellular uptake	[172]
	PEI	B-2 AR gene	60 nm	Bltw: CD1(ICR) mice	Increased alveolar fluid clearance	Safe, and effective gene therapy	[220]
	NEM	DMS	19.8 nm	Sprague–Dawley Rats	Reach deeper lung tissues	High anti-ALI effect	[173]

Abbreviations: CFC, 5(6)-carboxyfluorescein; CTG, capric/caprylic triglyceride; DMS, Dimethyl silicone; DPC, Dipalmitoyl phosphatidylcholine; DOPE, Dioleoyl phosphatidylethanolamine; EpoR, pulmonary erythropoietin receptor; SSM, Sterically Stabilized Phospholipid Nanomicelles; NPs, Nanoparticles; TPCA1, (2-[(Aminocarbonyl)- amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide; SPION, Superparamagnetic iron oxide nanoparticles; GP, 3-O-β-D-glucopyranosyl latycodigenin; HVEC, Human vascular endothelial cell line; ICAM, Intercellular adhesion molecule-1; Lev, Levofloxacin; NANA, *N*-acetylneuraminic acid; NLC, Nanostructured lipid carrier; NEM, Nanoemulsions; PAMAM, 3 poly(amidoamine); PEG, Polyethylene glycol; PEC, Poly(ε-caprolactone); PEI, Polyethyleneimine; PLGA Poly-lactic-co glycolic acid; PS, polystyrene; SMS, Poly(ε-caprolactone).

[155]. The designed liposomes have been shown to accumulate a considerable amount of drugs in the inflamed alveolar masses [53,157]. Besides, these drug delivery systems can be loaded with more than one drug molecule and enable them to reach selective therapeutic targets [17].

5.3. Gold nanoparticles

Although metal nanoparticles like gold are associated with the production of oxidative stress and toxicity, gold nanoparticles (GNPs) are considered as an excellent drug-delivery vehicle for ARDS at least at the preclinical level [159–161]. GNPs are widely considered as an effective nanocarrier because of their biocompatibility, comparatively easier preparation methods, and their tendency to bind with thiols and amines [163]. GNPs possess antioxidative and anti-inflammatory properties, which is why they have also been investigated in tissue injury models such as ARDS [159,160]. The peptide-encapsulated GNPs have been shown to potentially reduce lung injuries and modulate inflammation both in vitro and in vivo [165]. In acute lung injury mouse models, the peptide-GNP hybrids have reduced lung injury and inflammation by increasing regulatory T cells [167]. GNPs are considered as an essential mediator of Toll-like receptor-4 (TLR-4) signaling and oxidative stress generation hence, it helps in determining the severity of ARDS [39]. Peptide-conjugated gold NPs have been found to inhibit TLR-4 signaling pathways by modulating the process of endosomal acidification [166]. In a different study, incorporating hexapeptides to the GNP surface imparted anti-inflammatory activity and allowed rapid clearance in vivo [167].

5.4. Dendrimers

Dendrimers are another class of chemically synthesized star-shaped NPs gaining considerable popularity in the field of pulmonary nanomedicine [168]. Several dendrimers such as polyamidoamine (PAMAM), Poly(L-lysine) (PLL), polypropylenimine (PPI), and phosphorus dendrimers have been applied in the drug-delivery to pulmonary tissues. These drug-delivery vehicles mainly help in enhancing cellular uptake of conjugated drug molecules [169]. Surface-modified dendrimers have also been employed to efficiently deliver siRNA in vivo in the ARDS models [169].

5.5. Miscellaneous

Apart from the NPs mentioned above, other nanocarriers such as glycyrrhizin, polystyrene, oleic acid, and polyethyleneimine have been studied in the ARDS experimental models [48,170–172]. Oleic acid NPs have shown a substantial reduction of disease symptoms and a significant decrease in the oxidative stress levels of stimulated neutrophils. The glycyrrhizin NPs can be considered as an excellent anti-inflammatory agent [48,170,171]. Additionally, polystyrene NPs can readily cross the alveolar epithelium and deliver bioactive ingredients to specific targets [172]. Other groups of NPs, such as nanovesicles and nanoemulsions, have also been tested preclinically in the ARDS models. The nanovesicles and nanoemulsions-based aerosols performed way better than the convenient formulations [173]. Nanovesicles have been found to improve the resistance of pulmonary surfactants which is rendered ineffective due to ARDS-caused lung injury. It significantly improved the alveolar protein leakage and improved airway patency [119].

6. Conclusion

The field of nanomaterials is revolutionizing the future of pulmonary medicine by presenting various nanoscale delivery systems incorporated with drug moieties, peptides, and nucleic acids. It has shown great promise in the treatment of lung diseases, including ARDS. Fabrication of biodegradable drug-delivery systems through PEGylation and nano micelles formation has proved to be very helpful in evading RES and endocytic degradation machinery and overcoming physiological barriers caused due to respiratory mucous/alveolar fluids [119,120,174,175]. Nevertheless, the challenges associated with the clinical translation of these preclinically tested nanoformulations cannot be undermined. Long-term risk of excipient toxicity and nanoscale carrier are issues that need to be considered in the successful product development of pulmonary drug delivery systems [89]. Fine-tuning the NPs in terms of surface charge to enhance drug-deposition in the lungs and prolong the renal clearance of the nanoformulations and size is equally important, particularly in ARDS [177].

The particle size of drug delivery systems is crucial as the administration of large particles (>5 μm) have been reported to cause fatal health problems such as pulmonary embolism while too small particles are exhaled away from the human body [174]. Furthermore, a change in the diameter from 120 nm to 250 nm has a great impact on the mobility of NPs in mucosal airways. Moreover, anionic and hydrophilic surface properties reduce the possibility of RES recognition of NPs to a great extent [178]. Synthesis of sugar-coated NPs to target lectins present on the airway epithelial cells may prove to be useful in cell-specific targeting of NPs. Finally, more preclinical improvements in the pulmonary application of NPs considering health conditions like allergy and lung cancer would warrant translation of existing drug delivery systems for clinical evaluation.

7. Future perspectives

The clinical translation of these nanoformulations needs more therapeutically relevant research studies, which is difficult at present due to factors such as dearth of an ideal animal model for ARDS, poor health of patients due to multiple organ dysfunction, and the involvement of multiple pathways in the complex ARDS pathophysiology [3,93,179–182]. A profound understanding of ARDS pathophysiology and pathogenesis is needed to narrow down the gaps between the experimental results and the clinical realities and design more effective nano-therapeutics in the future. Understanding the fate of NPs and their interactions with biological systems and pulmonary tissue delivery of NPs in a completely stable form without any agglomeration and loss of drug requires further exploration [20,100,183]. Though inhalable nanocarrier systems allowed increased penetration to the lung tissues without any significant loss of drugs, improvement in terms of lung-site deposition efficiencies remains a necessity [120]. These can be further improved by optimizing aerosol characteristics and inhalation conditions as well as improving in terms of chemical stability, particle agglomeration, settlement, and pre-determined drug release. Finally, the role and safety profile of the NPs need to be further ascertained, and efforts towards lowering the toxicity of the nanoparticulate vehicles should be encouraged.

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CRediT authorship contribution statement

Pragya Prasanna: Conceptualization, Writing- Original draft preparation, Data curation. Shweta Rathee: Writing- Original draft preparation, Data curation. Arun Upadhyay: Writing- Reviewing and Editing. Sulakshana Sulakshana: Conceptualization, Supervision, Writing-Reviewing and Editing. All named authors are responsible for the final approval of the version to be submitted and are accountable for all aspects of the study. All authors have read and approved the final manuscript.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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