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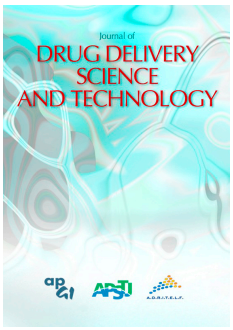

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PII: S1773-2247(23)00874-2

DOI: https://doi.org/10.1016/j.jddst.2023.105022

Reference: JDDST 105022

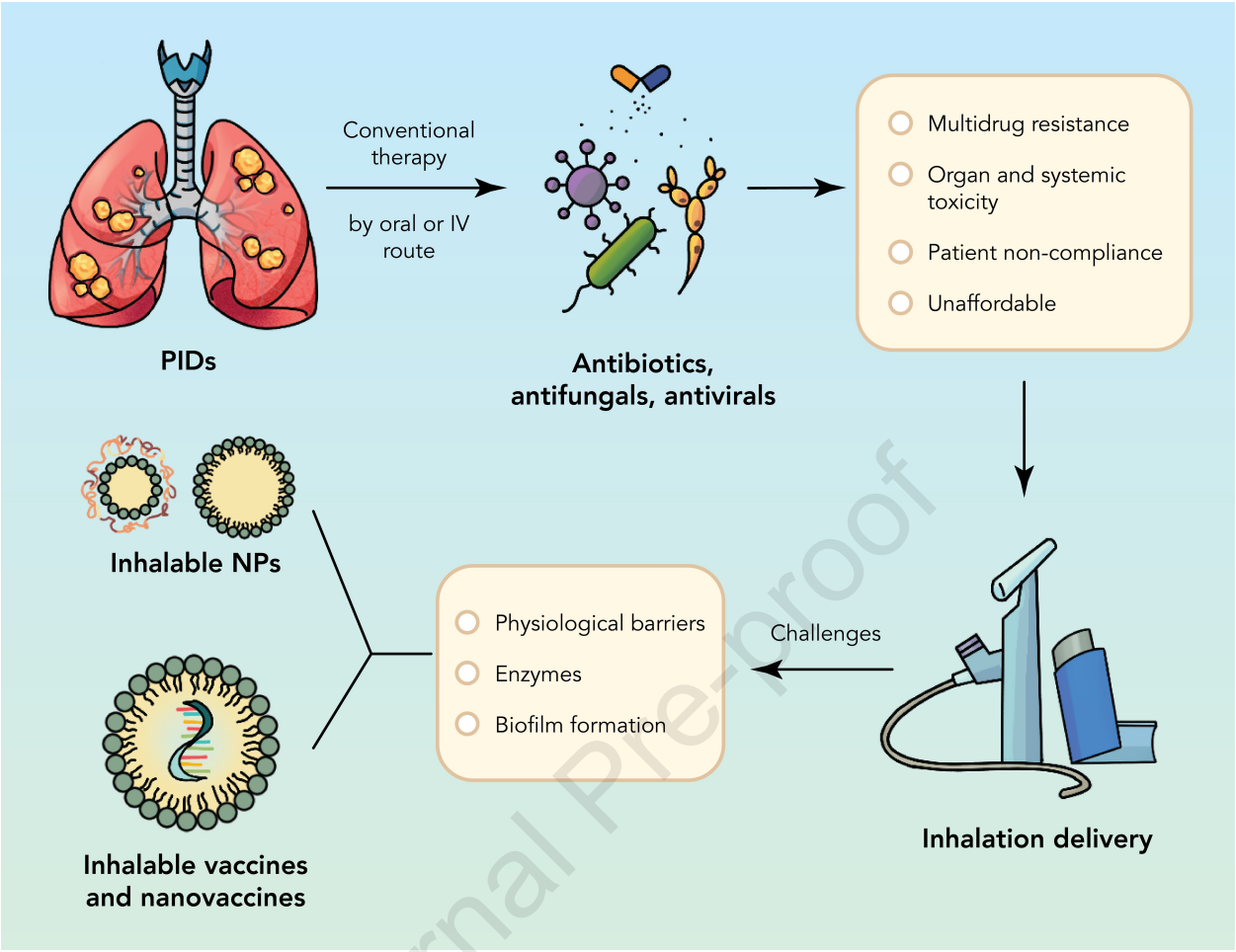
To appear in: *Journal of Drug Delivery Science and Technology*

Received Date: 27 July 2023

Revised Date: 8 September 2023

Accepted Date: 29 September 2023

Please cite this article as: P. Kumbhar, J. Kaur, G. De Rubis, K.R. Paudel, P. Prasher, V. Patel, L. Corrie, D.K. Chellappan, G. Gupta, S.K. Singh, V. Patravale, J. Disouza, K. Dua, Inhalation drug delivery in combating pulmonary infections: Advances and challenges, *Journal of Drug Delivery Science and Technology* (2023), doi: https://doi.org/10.1016/j.jddst.2023.105022.



Inhalation drug delivery in combating pulmonary infections: Advances and challenges

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Inhalation drug delivery in combating pulmonary infections: Advances and challenges

Abstract

Pulmonary infections (PIs) are contributing as a significant cause of mortality across the world. The clinical applications of a variety of therapeutics approved for PIs have been limited owing to their fatal side effects and inappropriate route of administration. The aforesaid drawbacks can be conquered *via* the inhalation delivery of therapeutics. Inhalation drug delivery can be a promising approach for targeting PIs. This approach can deliver drugs to the target site and minimize toxicity. However, types of barriers are the chief hurdle to inhalation drug delivery. The nanoparticulate approach can be efficient to overcome these barriers. The various inhalable nanoparticles (NPs) such as lipidic, polymeric, hybrid lipid polymer (HLP), and metal NPs have been explored to treat PIs efficiently. Vaccines and nanovaccines have also shown promise in the prevention and treatment of PIs and can be further explored. The inhalation device is a core of inhalation drug delivery however these devices are allied with several drawbacks therefore; the apt selection of inhalation devices is of huge significance. Furthermore, very few inhalable formulations to treat PIs have been marketed and entered into clinical trials, and extensive efforts are required to bring more formulations into the market and clinical trials. In this review, the author discusses PIs overview, conventional treatment for PIs and their limitations, inhalation drug delivery benefits and challenges. Further, nanoparticulate-based inhalation drug delivery, inhalable vaccines and nanovaccines, inhalation devices, and inhaled formulations in market, and clinical trials are also discussed. In a nutshell, inhalation drug delivery can be a promising strategy to manage PIs.

Keywords: Pulmonary infections; inhalation drug delivery; nanoparticles; nano vaccines; clinical trials; inhalation devices

1. Introduction

Pulmonary infections (PIs) are a significant group of infection that seriously endangers human life and world health. Among the PIs, pneumonia was observed to be a chief cause of mortality in children. WHO reported around 15% of death of children below 5 years due to pneumonia in 2017 across the globe. Tuberculosis (TB) is noticed to be the top 10 causes of mortality globally [1]. Recently, COVID-19 lead to an enormous increase in mortality rates globally. Thus, globally, PIs have a significant negative social and economic impact. Treating these PIs caused by novel bacteria, viruses, and fungi is highly challenging.

The anti-infectious therapeutics including antibiotics, antiviral, and anti-fungal are reported against PIs [2]. However, the conventional delivery of these therapeutics *via* oral or intravenous routes required high dose and dosing frequency that leads to microbial resistance against therapeutics [3- 4]. Further, the overuse of these anti-infectious agents caused fatal side effects including cardiotoxicity, and contributes to resistance to their effect [5].

The above problems necessitate the apt delivery of therapeutics to treat PIs efficiently. Inhalation (pulmonary) delivery is an important avenue that allows delivering drugs to the target region of the lung that result in quick onset of action with significant efficacy at lower doses [6]. The other chief benefits of this approach are the large absorption area that results in rapid absorption and permeation of therapeutics. Reportedly, site-specific delivery can minimize systemic and organ-related toxicities [7]. However, the main bottlenecks in inhalation delivery are the physicochemical properties of cargo and the physiological barriers. The physicochemical properties such as solubility, molecular size, and protein binding are key contributors influencing cargo permeability in the lung. Further, physiological barriers such as the presence of enzymes cause the degradation of drugs. Some natural protective mechanisms such as the presence of mucociliary and phagocytic can clear the particles with a size of more than 6 μm devoid of their interaction with lung tissues, which results in failure of therapy [8-9].

The sorts of aforementioned challenges in the path of inhalation delivery can be overcome *via* nanoparticulate-based delivery of drugs [10]. The nanoparticulate-based delivery confers a range of benefits including reduced degradation and clearance by the enzymes, and enhanced residence time in the lung. In addition, surface modification of nanoparticles (NPs) decreases the phagocytosis-mediated clearance of the drug thereby improving stability and therapeutic efficacy

[10-11]. Further, vaccines and nanovaccines have also shown promise in the prevention of PIs caused by various pathogens.

The present review broadly discusses the inhalation-based delivery of drugs to treat a variety of PIs efficiently. The areas covered in the present review include; PIs overview, conventional treatment approaches to treat PIs and their associated limitations, and inhalation-based drug delivery benefits and challenges. The nanoparticulate-based inhalation drug delivery, inhalable vaccines, and nano vaccines employed to treat PIs are also briefed with some case studies. Further, inhalation devices and their challenges, conventional and advanced formulations marketed or undergoing clinical trials for PIs are also discussed.

2. Pulmonary infections overview

PIs are caused by various infectious pathogens such as viruses, bacteria, and fungi. This includes various pathogenic strains such as *influenza*, SARS-CoV-2, respiratory *syncytial* virus (RSV), tuberculosis, *aspergillus, cryptococcus, pneumocystis*, endemic fungi, and so on [11-12]. The sorts of PIs caused by these pathogens are pneumonia, influenza, tracheitis, sinusitis, bronchitis, cystic fibrosis, COVID-19, TB, etc (Fig. 1). Pneumonia is a well-known lung infection caused by several kinds of viruses, bacteria, and fungi in all age groups that primarily affects the alveoli and distal airways. It is a global health burden linked with high morbidity and mortality. It is classified as community-acquired pneumonia and hospital-acquired pneumonia [13]. The influenza virus, adenovirus, RSV, and parainfluenza are the most prevalent causes of viral pneumonia in infants. Juvenile viral pneumonia is brought on by the influenza virus and the rhinovirus [14]. The most common bacteria responsible for community-acquired pneumonia are *Streptococcus pneumoniae* and *Haemophilus influenzae*. *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Moraxella catarrhalis* are among the most virulent bacteria that frequently produce hospital-acquired pneumonia [15]. Methicillin-resistant *Staphylococcus aureus* and *Enterobacteriaceae* are mainly contributing to ventilator and healthcare-allied pneumonia [16]. Further, the most prevalent fungi responsible for fungal pneumonia are *Pneumocystis*, *Cryptococcus*, and *Aspergillus* [17]. Patients with pneumonia experience uncomfortable respiratory and systemic symptoms such as cough, difficulty in breathing, increased heart rate, heartbeat, fever, sweating, and chill. The diagnosis is dependent on clinical presentation and radiological findings. Accurate identification of causative agents is crucial to planning antimicrobial therapy for pneumonia and preventing antibiotic resistance.

Effective management of pneumonia involves accurate diagnostic tests and therapies that include both antibiotic and non-antibiotic medicines [13].

Influenza is an infection common to birds and mammals caused by the influenza virus that belongs to the RNA virus family *Orthomyxoviridae*. During the recent pandemic years, there were reports of 3-10 million populations being infected with influenza resulting in the death of 250,000-550,000 due to the seasonal spread around the world [18]. When a virus enters the respiratory tract, the innate and adaptive immune responses of the host respond to protect against the virus and facilitate the repair of affected tissue to prevent further damage. However, dysregulated host immunity results in massive cytokines release and/or leads to chronic tissue sequelae [19]. For example, mice infected with influenza virus A (H1N1) have shown remarkably increased levels of interleukin-13 (IL-13) expression in their lungs [20] suggesting IL-13 as a crucial therapeutic target against influenza-induced exacerbation of chronic lung diseases [21]. Investigation involving animal models such as mice is crucial to recognizing the biological and genetic factors contributing to influenza infection and validation of biomarkers from human studies. Nevertheless, human and mouse cross-species resemblance is frequently argued owing to the fact that pre-clinical animal models focus on the infected lungs, while human studies primarily use peripheral blood (not lungs) for analysis. Moreover, human/clinical investigation does not appraise genetic background as a variable even though humans are genetically diverse. Kollmus et al., studied a cross-species gene expression of the influenza-infected patient's peripheral blood and influenza-infected mouse. The results highlight that alterations of gene expression in individual genes are mostly identical in both species. The lead genes in humans were found to be differentially regulated in mice concluding that the pre-clinical experimental models are very important to verify and to uncover potential genes that could serve as biomarkers for us [22].

Bacterial tracheitis is an infection of the trachea causing dyspnea and stridor. This infection is caused by various bacteria such as *Staphylococcus aureus*, *Streptococcus pneumonia*, *Moraxella catarrhalis*, and *Hemophilic influenza*. It is observed in both infants and adults [23-24]. According to estimates, there is 0.1 to 1 incidence of bacterial tracheitis for every 100,000 children worldwide each year [25]. The sinusitis (rhinitis) of acute, subacute, and chronic types is caused by a range of viruses including adenovirus, influenza, parainfluenza, and RSV. The bacteria causing acute bacterial sinusitis are *Staphylococcus aureus*, *Streptococcus pneumoniae*,

Haemophilus influenzae, and *Moraxella catarrhalis* [26]. Additionally, fungi like *Candida* and *Aspergillus* also contribute to sinusitis infections. This infection is mainly allied with nasal congestion and facial pain [26]. Acute bacterial sinusitis accompanies about 7.5% of upper respiratory tract infections in children of all ages [27]. Similarly, bronchitis is a lung airway inflammation associated with wheezing and chest congestion. This infection is mainly caused by adenovirus, parainfluenza virus, and influenza A and B virus and it account for 85-95% of instances of acute bronchitis. Bacteria such as *Streptococcus pneumonia*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Mycoplasma pneumonia* are chiefly responsible for bronchitis [28]. Cystic fibrosis is another serious PIs caused by both bacteria and viruses. The common bacteria involved in cystic fibrosis infection are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Haemophilus influenza*. Besides, influenza type A and B virus, parainfluenza, RSV, and human rhinovirus are recognized as viral pathogens contributing to cystic fibrosis. Cystic fibrosis causes damage to the lungs, digestive system, and numerous body organs, and also affects cells involved in mucus formation [29-30].

SARS-CoV-2 is another viral strain that causes the infection of the lungs. The recent information on the prolonged effects of COVID-19 pneumonia on the lungs has been disseminated by various literatures. SARS-CoV-2-infected patients with moderate-to-severe pneumonia develop abnormalities ranging from parenchymal bands to bronchial dilation to frank fibrosis [31]. During SARS-CoV-2 infection, the synergism of two key cytokines; TNF-α and interferon (IFN)-γ triggers inflammatory cell death, tissue damage, and cytokine shock syndrome [32] suggests that inhibiting the cytokine-induced inflammatory cell death signaling pathway may be beneficial with COVID-19 infection. Various vaccines, drugs, vitamins, and nutraceuticals are being investigated for the prevention or targeting of different symptoms associated with COVID-19 infection [33-34]. Some studies have highlighted the correlation between autoantibodies detected in SARS-CoV-2-infected patients and the severity of the disease. Therefore, the use of autoimmune medications could be another approach to managing the infection [35].

TB is a threatening contagious disease caused by a bacterial strain; *Mycobacterium tuberculosis* (MTB). TB not only affects lungs (80% of total TB cases) but can also other tissue/organs termed extrapulmonary. After entry of MTB into respiratory system, they reach deep inside the lungs to the bronchioles and alveoli. The bacteria first stimulate polymorph nuclear leukocyte reaction then they are engulfed by alveolar macrophage. The bacteria can grow

inside macrophages resulting in an inflammatory cascade reaction and further worsening the condition because of cytokines and chemokines known to attract immune cells such as natural killer (NK) cells, neutrophils, dendritic cells, and lymphocytes from the circulation to the lungs [36]. One of the issues associated with the management of TB infection is the multi-drug resistance strain where traditional medicines are not very effective to cure it. In this regard, researchers are motivated to find novel therapeutic agents including those coming from nanotechnology such as anti-tubercular drugs loaded in solid lipid NPs (SLNPs) [37].

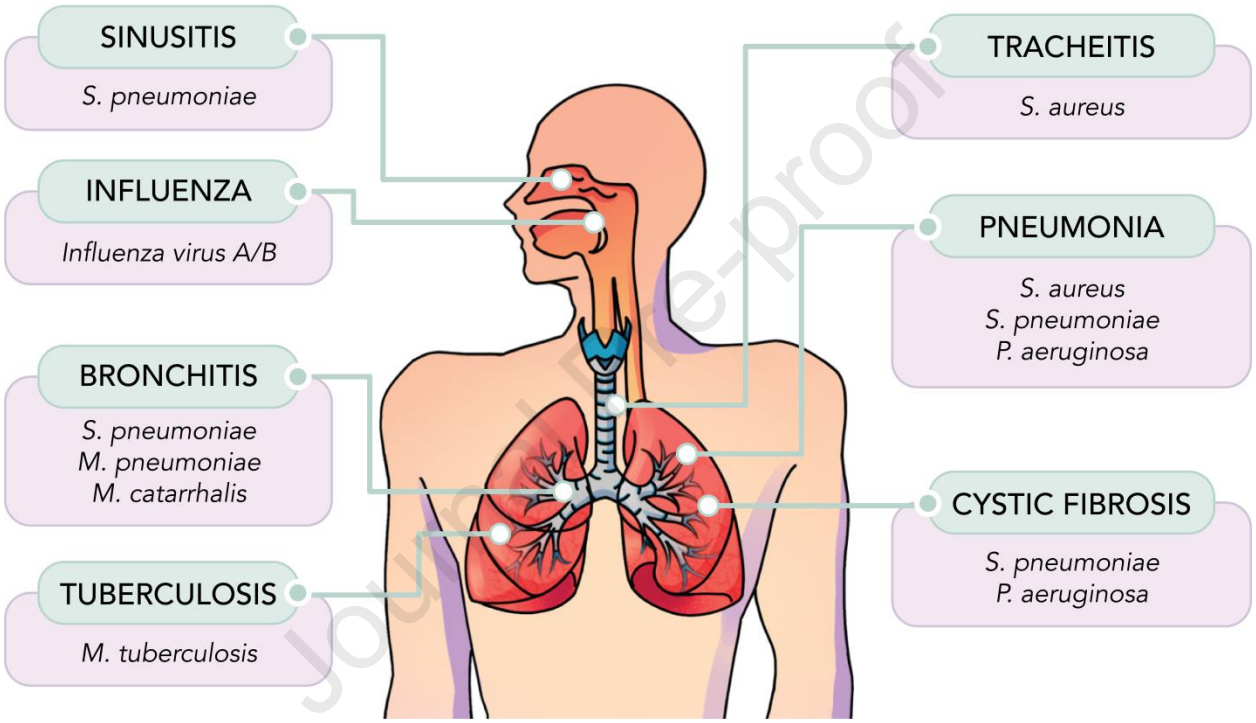


Fig. 1: An overview on pulmonary infections

3. Current treatment strategies for PIs and their limitations

The commonly employed treatment strategy for PIs includes antibiotics, antiviral, and antifungal therapeutics, and their combinations. Large molecule drugs including proteins and peptides are also used to treat PIs [38]. The sort of antibiotic selection depends on the infection severity, complications associated, and the age of the patient [39].

The antibiotics from various classes used to treat PIs are β-lactams (amoxicillin and cephalosporin), tetracycline (doxycycline), macrolides (azithromycin and clarithromycin), cephalosporins (cefuroxime and cefpodoxime), fluoroquinolones (moxifloxacin, gemifloxacin, ciprofloxacin, zabofloxacin, delafloxacin, and levofloxacin), nonfluorinated quinolone

(nemonoxacin), etc [40-41]. In addition, isoniazid, rifampicin, ethambutol, and pyrazinamide antibiotics are employed for treating PIs including TB [42]. The anti-viral therapeutics from different classes employed to treat PIs include neuraminidase inhibitors (oseltamivir, peramivir, and laninamivir), matrix-2 protein inhibitor (rimantadine and amantadine), etc [43]. Furthermore, posaconazole, itraconazole, fluconazole, voriconazole, and isavuconazole are used to treat PIs caused by the fungi [44].

These above-mentioned therapeutics are used by both oral and parenteral routes for 7-10 days depending on the severity of infections. However, conventional (oral) therapy is observed to be inefficient in regaining baseline lung infection due to the improper concentration of medicines at the target site that resulted in bacterial resistance against antibiotics [45]. Additionally, oral therapy of antibiotics requires frequent administration in high doses which also causes bacterial resistance to antibiotics [46]. Further, the delivery of antimicrobial therapeutics through oral or parenteral routes causes poor therapeutic distribution at the target site. Most of these infections including TB require antibiotics in combination which produces systemic and organ-related side effects. The range of negative effects reported with conventional use of these therapeutics includes neurotoxicity, hepatotoxicity, hypertension, abdominal pain, alopecia, hypokalemia, hyperuricemia, dizziness, etc [42-44]. Reportedly, frequent doses and long-term therapy may result in the withdrawal of therapy by the patient causing microbial drug resistance [47]. Further, the unaffordable costs of antibiotics and patient non-compliance are other significant limitations in their use [48].

Biologics including monoclonal antibody (mAb)-based therapeutics, nanobodies, anti-microbial or anti-viral peptides, and peptide-like therapeutics demonstrated significant promise in the management of PIs [49-51]. The nanobodies demonstrated effectiveness against infection caused by influenza virus [49]. Several, intravenously administered mAbs such as casirivimab and imdevimab are employed for treating COVID-19 [50]. Anti-microbial peptides such as defensins, cathelicidins, hepcidin, transferrins, etc have been employed to treat PIs like COVID-19 [51]. Furthermore, human neutrophil peptides, human β-defensins, retrocyclins, urumin, etc were used against influenza infection whereas RSV infections have been treated with human-defensin and helical peptide (LL-37) [52]. The intravenous administration of these therapeutics was reported to be ineffective in delivering drugs to the lungs [53]. Another major obstacle in using biologics by the conventional route is their rapid removal from the body through renal

filtration. This rapid clearance might necessitate repeated biologic injections, increasing therapy costs and patient non-compliance [54]. Notably, the intravenous administration of biologics allied with various negative effects. For instance, casirivimab and imdevimab exhibited adverse effects like swelling, bleeding, pain, and infection at the site of injection following intravenous use to treat COVID-19 [50].

4. Importance of inhalation-based drug delivery (IBDD) for PIs treatment

The diverse limitations in the path of conventional treatment strategies for PIs as mentioned above necessitate their delivery *via* the apt route of administration. Pulmonary or IBDD of antimicrobials can be a promising way to overcome the bottlenecks associated with their oral and parenteral delivery. This IBDD delivers drugs locally at the infected site in the lung affecting bacterial load and reducing the dose and dose frequency of the drug. This reduction in dose and dose frequency of therapeutics may contribute to reducing side effects and microbial resistance [55-56]. Despite these advantages, a downside of IBDD is the rapid systemic absorption of many drugs occurring at the pulmonary level, which often results in a short residence time of the drug in the lungs and therefore low pulmonary exposure. To increase pulmonary exposure to the drug, and therefore further limit side effects originating from systemic exposure, a variegated range of strategies can be applied. These include the modification of the active principle or its conjugation with polymers, to reduce the pulmonary absorption rate and, most importantly, the formulation of the active principles in different types of NPs. The different approaches that can be applied to extend the pulmonary exposure of inhaled drugs have been reviewed extensively by Guo et al. [57].

This IBDD model is proven for the delivery of biologics, which are otherwise administered intravenously. The pulmonary delivery of biologics is a non-invasive administration mode for the local or systemic delivery of biologics. Furthermore, this administration route enables the delivery of biologics at high concentrations to the lung tissues. The pulmonary route of administration also reduces the likelihood of biologics degrading as a result of first-pass metabolism and the activity of the proteolytic enzyme, making it a substitute for more intrusive ways to accomplish considerable concentration of therapeutics at lung in reduced doses. However, it is not very popular owing to the insufficient stability of proteins during aerosolization and in the physiological environment of the lungs. The application of nebulizers for dry powder administration is another suitable strategy for reaching an improved delivery of

biologics by minimizing the shear stress [58]. In order to administer the dry powder biologics through a nebulizer, they are first suspended in physiological saline or phosphate-buffered saline [59-60]. For instance, Hufnagel et al., delivered freeze-dried monoclonal antibodies using nebulizers after reconstitution with phosphate-buffered saline [59]. The sorts of benefits of IBDD over other delivery routes are depicted in Fig. 2.

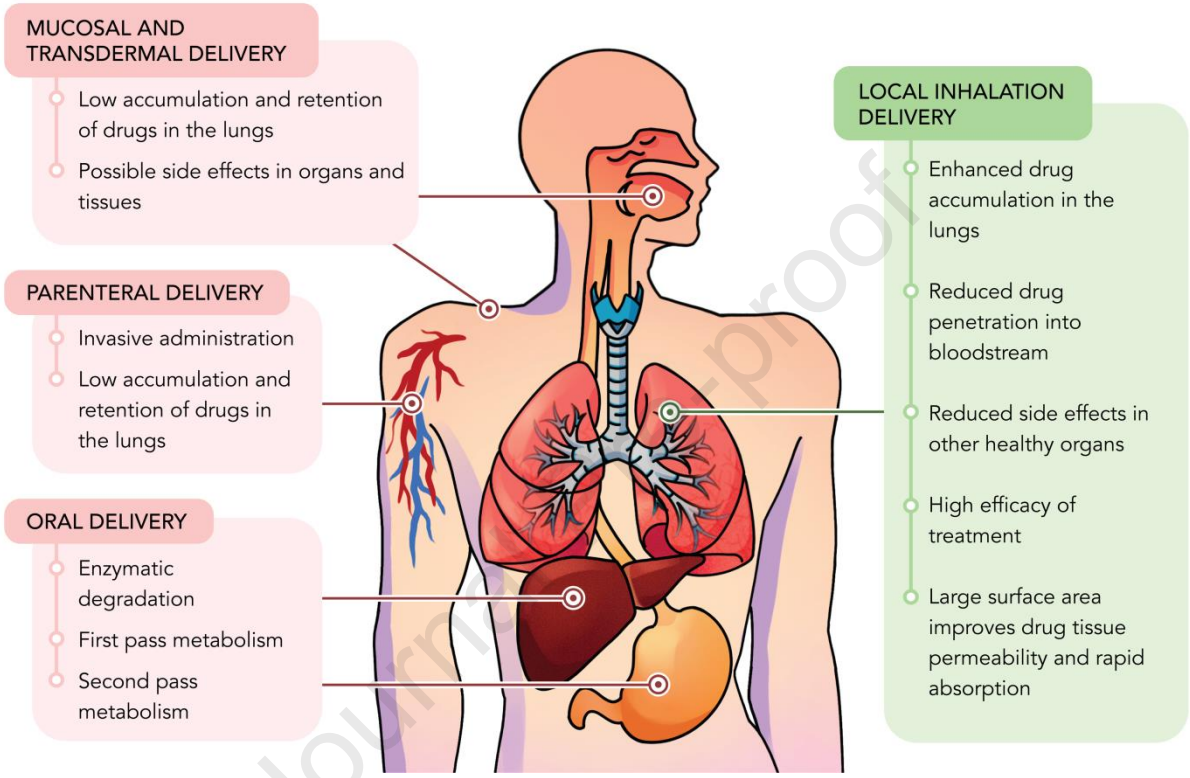


Fig. 2: Different benefits offered by IBDD over other administration routes

By considering the aforesaid benefits, Yapa et al., studied the systemic and pulmonary pharmacokinetics of colistin methanesulfonate after their intravenous and inhalation administration in treating cystic fibrosis. The nebulized colistin methanesulfonate was administered at 2 and 4 million international unit (IU) doses *via* inhalation route whereas 150mg of colistin methanesulfonate was administered through intravenous route in the patients with cystic fibrosis. The systemic availability of nebulized colistin methanesulfonate was only 7% and 5% at 2 and 4 million IU doses, respectively when compared to its intravenous administration. Additionally, the sputum concentration of nebulized colistin methanesulfonate was substantially higher than observed with its intravenous administration. Based on these findings, they came to the conclusion that nebulized colistin methanesulfonate systemic availability might be

significantly reduced, which would lower the dose, dosing frequency, and systemic adverse effects [61].

The cohort study by Almangour et al., in the adults, investigated the benefits of colistin delivery *via* inhalation routes in comparison to intravenous route in treating pneumonia. The patients who participated in their study received intravenous colistin alone or in amalgamation with aerosolized colistin. They observed significant clinical cures in about 65% of the patients with aerosolized plus intravenous colistin therapy than with alone intravenous colistin therapy (clinical cure in only 37% of patients). Additionally, they found that administering colistin by inhalation resulted in noticeably better penetration, lower systemic exposure, and less nephrotoxicity [62]. In another intriguing cohort study, the Leache and team assessed the impact of nebulized antibiotics (amikacin, gentamycin, tobramycin, and colistimethate) delivery in combination with their intravenous delivery against pneumonia. They compared the consequences of combined nebulized and intravenous antibiotics delivery with their intravenous delivery alone on renal toxicity. In comparison to intravenous antibiotic treatment alone, they noticed a decreased risk of kidney toxicity after nebulized and intravenous antibiotic dosing [63]. Moreover, Wang and co-workers explored the targeting behaviour of respirable microparticles of azithromycin for treating pneumonia. The main objective of their study was to achieve local delivery of azithromycin in the lung and lessen the off-targeted side effects. These azithromycin-laden respirable microparticles demonstrated 3.5 times higher accumulation and enhanced retention in the lung when compared to its oral and intravenous administration [64].

Similarly, Cong and team evaluated the anti-inflammatory effects and pulmonary pharmacokinetics upon intratracheal and intravenous injection of traditional Chinese medicine 'Chuankezhi' (CKZ) which is used for the treatment of respiratory disorders. It was reported that the aerosolized formulations of CKZ that were generated with a commercial nebulizer showed commendable aerodynamic properties. The administration of CKZ *via* the intratracheal route increased the lung-to-plasma concentration ratio of icariin and epidemins A, B, and C by 25-718-fold compared to the intravenous administration, which results in the amelioration of local anti-inflammatory effects by simultaneously reducing the fraction of active principles reaching systemic circulation and, therefore, the risk of adverse effects [65].

5. Challenges in pulmonary inhalation drug delivery

Despite noteworthy benefits, IBDD also possess some challenges. Two approaches can be used to deliver drugs *via* pulmonary delivery: intranasal delivery and oral inhalational delivery [66]. Concerning intranasal delivery, this route is often used for aerosols, and it is limited by the innate anatomical function of the nose as an inhaled particulate filter. As such, conventional aerosol droplets of size usually ranging between 3 and 7 μm, are effectively filtered by the nasal valve, while particles of smaller size between 0.5 and 3 μm, are filtered by the nasal mucosa and eliminated by the ciliated epithelium [67]. This has been shown to result in concentration loss levels as high as 85% and, for this reason, intranasal administration is not the advised route for pulmonary delivery [68].

A comparatively advantageous alternative is represented by oral inhalational delivery, whereby the concentration loss can be as low as 20% [66]. Despite this, oral inhalational drug delivery is limited by two main factors: the respiratory system's innate defense mechanisms, poor medication adherence, and incorrect usage of the inhaler device by patients [69-72]. The respiratory system's defense mechanisms are intended to prevent foreign materials from depositing on the epithelial surface of the respiratory system and to remove or inactivate any material that successfully manages to deposit on the epithelium. These barriers can be further classified into three categories: mechanical, chemical, and immunological barriers [73].

With regards to mechanical barriers, the first line of defense is in the upper airways, whose narrow angles and variable dimensions cause inertial impaction of inhaled particles, preventing their entry into the lungs [69, 74]. The particles that manage to successfully enter the lung encounter another mechanical barrier, constituted by the many bifurcations and progressive diameter restriction of the bronchial tree. This further limits the amount of drug potentially reaching the alveolated region, restricting drug delivery to the peripheral lung [69]. To overcome these initial barriers, allowing whole lung delivery and alveolar deposition, the ideal particle's aerodynamic diameter should be <3 μm [75]. Another fundamental mechanical barrier is represented by mucociliary clearance, in which particles are trapped by the secreted mucus and removed from the conducting airways by the beating cilia of the epithelium, which delivers the particulate matter to the oropharynx. Mucociliary clearance is considered to be the main innate mechanism of defense of the lung [76]. The impact of the aforementioned mechanical barriers on effective lung delivery is exacerbated in patients affected by inflammatory respiratory diseases

such as asthma and COPD, which are characterized by airway narrowing (bronchoconstriction) and mucus hypersecretion [77].

Upon deposition in the airway epithelium, particles and aerosol droplets dissolve in the airway fluids, where they release the administered drugs in solution [78]. Here, drugs encounter the lung's chemical barriers, constituted by the action of chemicals (enzymes) such as trypsin, cysteine proteases, serine proteases, metalloproteases, and cathepsin [69, 79]. This trypsin and proteases such as cathepsin H, cathepsin D, dipepidyl peptidase, angiotensin-converting enzyme and endopeptidase located on lung smooth muscle cells, alveolar and bronchial smooth muscle contribute to the degradation of antimicrobial peptide therapeutics including human neutrophil peptide, LL-37, and plectasin, which results in poor lung delivery [58, 80-82]. The pulmonary surfactants comprised of phospholipids and surfactant proteins A, B, C, and D also act as another chemical barrier in IBDD. These surfactants are responsible for the removal of therapeutics [83]. Additionally, the lung also contains enzymes including cytochrome (CYP)-450, monoamine oxidase, aldehyde dehydrogenase, flavin-containing monooxygenases, and nicotinamide adenine dinucleotide phosphate (NADPH)-CYP450 reductase, which act as an impediment in the delivery of therapeutics *via* inhalation [84-85].

Immunological barriers are represented by particle phagocytosis, which is mediated by alveolar macrophages, and it is the predominant clearing mechanism occurring in the lower airways, contributing to the clearance of particulate of size approximately ranging between 0.5 and 5 µm [86-87]. Upon phagocytosis, particles are either subjected to lysosomal degradation or removed *via* the lymphatic system [88]. Phagocytosis represents a double-edged sword in the inhalational delivery of drugs. On the one hand, it significantly contributes to drug removal and therefore it decreases the effective drug concentrations at the intended site [87-88]. On the other hand, in the case of infective diseases such as TB, in which the pathogenic microorganisms reside and replicate within alveolar macrophages, the macrophages represent the drug target and, therefore phagocytosis should be encouraged [89].

Furthermore, in the case of biologics, the development of inhalable formulations possesses a sizeable challenge in terms of the rational design of inhalable formulations, and the achievement of appropriate aerodynamic properties for their effective deposition in the lungs. Furthermore, the biophysical and anatomical barriers such as airway geometry, mucociliary and macrophage clearance, humidity, and the activity of alveolar macrophages are important considerations for

ensuring lung sterility. These factors also present a significant barrier to the determination of the therapeutic efficacy of inhaled formulations of biologics. Similarly, inhaled biologic therapy is challenging because it requires the latter to pass through the lung epithelia in order to reach systemic circulation and provide an ideal therapeutic impact [90].

Reportedly, biofilm a thick coating attached to an inert lung surface comprised of an extracellular polymer, polysaccharides, lipids, and DNA formed by lung-infected microbial cells serves as an important barrier affecting the penetration of antimicrobial therapeutics [91-92]. The diverse types of barriers in pulmonary inhalation drug delivery are shown in Fig. 3.

Taken together, the combined effect of mechanical, chemical, and immunological barriers poses a severe limit to the pulmonary or systemic bioavailability of most inhaled drugs, highlighting the urgent necessity to develop novel, more efficient inhaler systems or suitable formulation approaches to overcome these limitations [93].

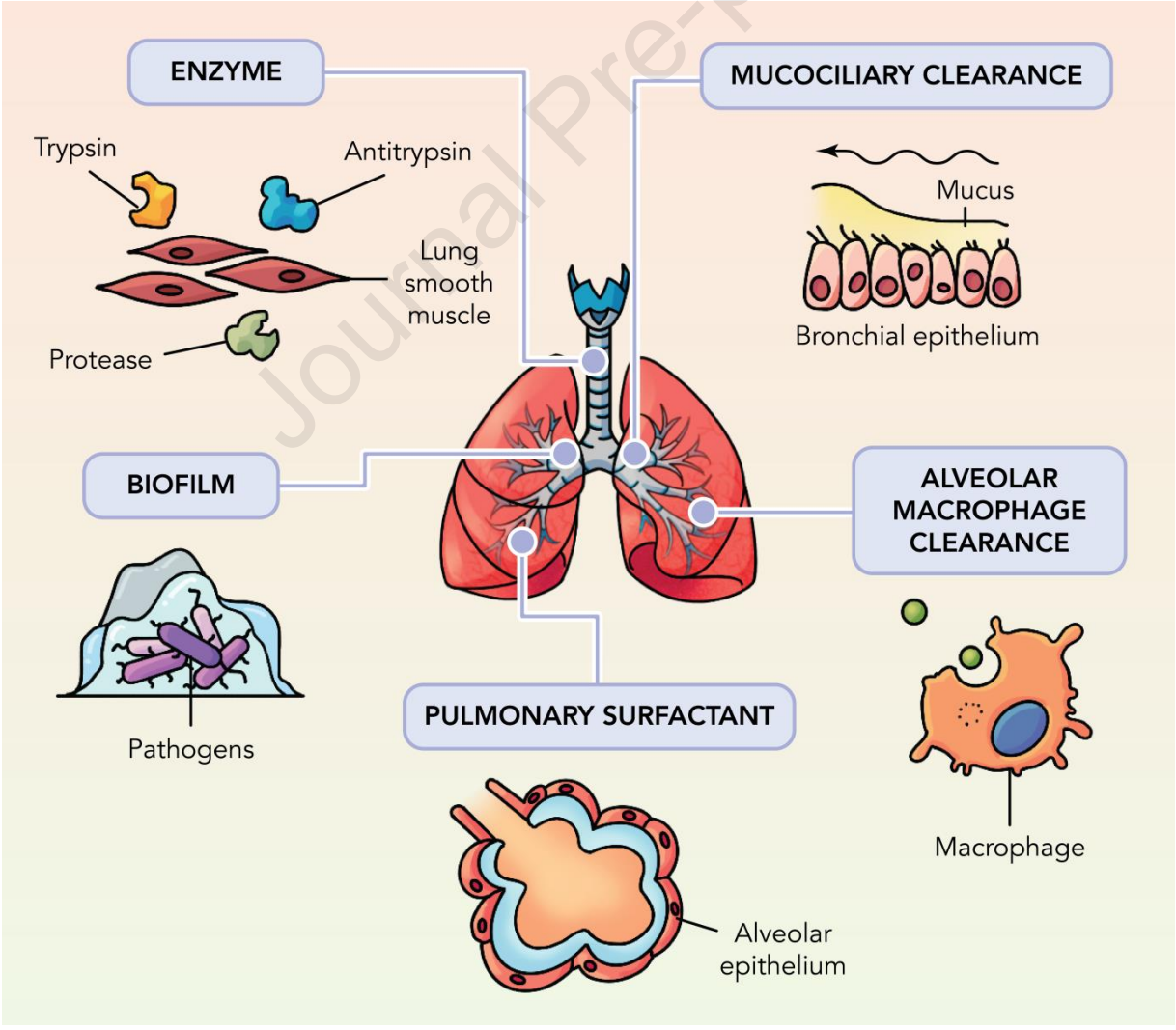


Fig. 3: Different types of barriers in pulmonary inhalation drug delivery

6. Nanoparticulate-based inhalable drug delivery systems for PIs

The challenges of pulmonary inhalation drug delivery described earlier severely limit the delivery of antibiotics, antifungals, and antiviral drugs through the inhalational route. The development of inhalable nanoparticle (NP)-based drug formulations represents a suitable option to overcome these limitations. NP-based formulations have many advantages. Firstly, the encapsulation of drugs in NP systems improves the drugs' solubility and stability, protecting the drugs from degradation and the lung's innate defense systems, and therefore enhancing the therapeutic effects [94-95]. Furthermore, NPs can be engineered *via* surface functionalization to allow targeted delivery to the deep lung regions, maximizing the amount of drug that reaches the site of infection [96]. Surface functionalization of NPs with lung surfactants was reported to decrease phagocytosis. Other types of functionalization also allow for achieving sustained release of the drugs over an extended time, resulting in a longer duration of therapeutic effect while simultaneously reducing the frequency of administration and enhancing patient compliance [97-98]. Finally, NP-based systems are advantageous in preventing multi-drug resistance, which is a common complication of PIs [99], as they allow the delivery of combinations of drugs [100]. Due to the many advantages offered by using NP-based formulations, numerous researchers all over the world are working on the development of NP-based inhalational formulations for the treatment of PIs. The diverse nanoparticulate-based approaches used in the inhalation delivery of drugs to treat PIs are depicted in Fig. 4. A few relevant case studies concerning the above-mentioned delivery systems are presented in Table 1.

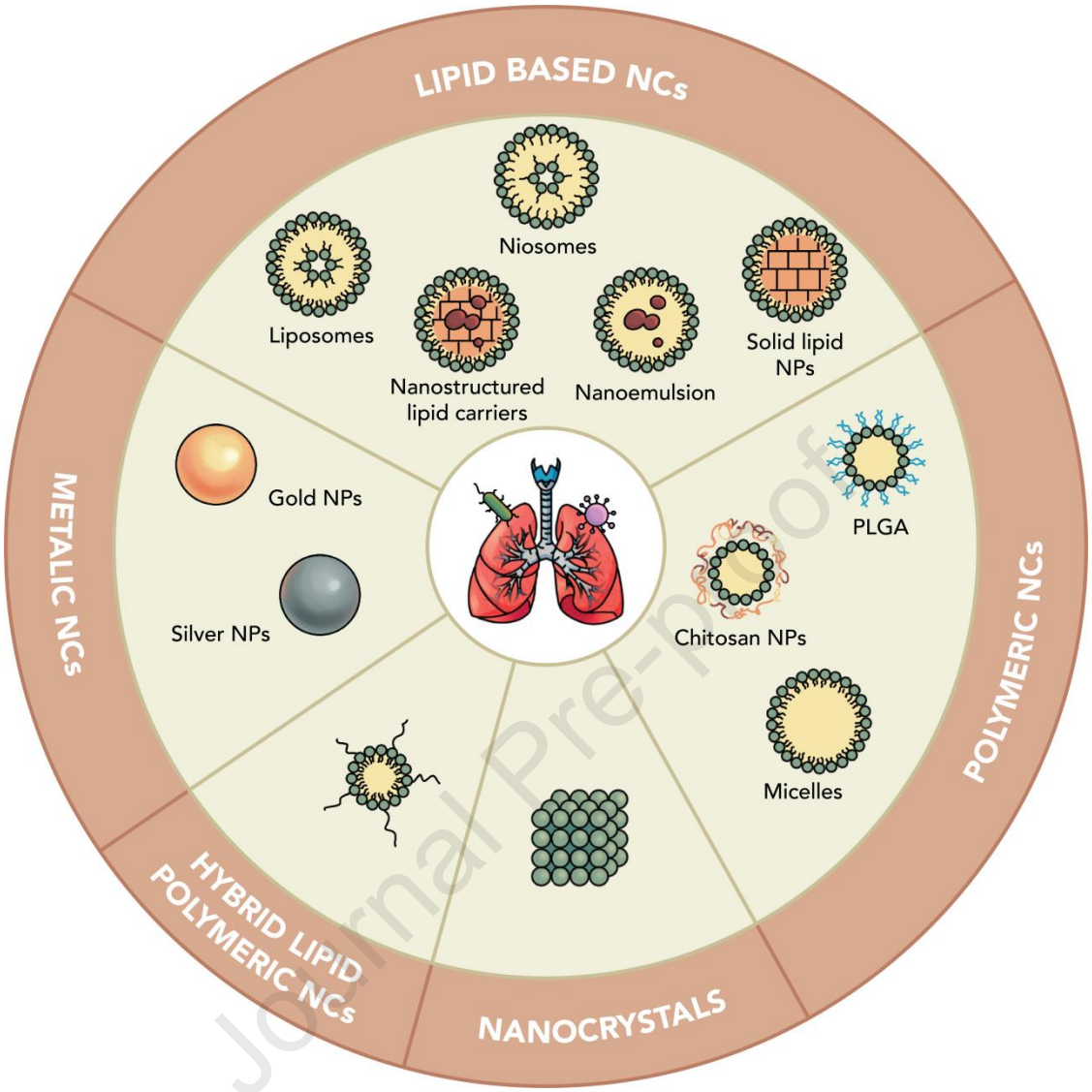


Fig. 4: Nanoparticulate-based approaches used in the inhalation delivery of drugs to treat PIs

6.1. Lipid-based NCs

Lipid-based drug delivery systems (LDDS) have gained importance due to their ability to deliver poorly water-soluble drugs. LDDS are widely preferred over conventional dosage forms because of their multifunctional role, good biocompatibility, and biodegradability [101]. In addition, LDDS offers desire-release kinetics such as controlled, sustained, or extended [102]. These lipid-based formulations are generally composed of water-insoluble excipients, triglycerides, surfactants, co-surfactants, co-solvents, simple oils, or a mixture of oils and many lipids [101]. LDDS can be formulated to enhance the absorption of drugs by reducing the particle size to the molecular level and increasing drug transport to systemic circulations by altering enterocyte-based transport [103]. However, considering that the systemic absorption of inhaled drugs used

for the treatment of PIs is usually not desirable, LDDS can also be formulated to achieve a sustained release of the active principle, and therefore improve pulmonary exposure to the active principle while simultaneously reducing the levels of drug reaching systemic circulation [57, 104]. Apart from this, LDDS can be solidified into powder or pellets using various techniques pertaining to its stability for oral delivery. The most commonly explored and established LDDS include liposomes [105], niosomes [106], self-nano emulsifying drug delivery systems (SNEDDS) [107], and solid lipid nanoparticles (SLNPs) [108].

6.1.1. Liposomes

Liposomes are spherical vesicular nanostructures composed of one or more partially substituted phospholipid bilayers along with cholesterol [109]. It consists of a hydrophilic aqueous core and hydrophobic phospholipid tail, so it can encapsulate hydrophilic and lipophilic drugs [110]. This composition of liposomes facilitates its use in encapsulating various categories of payloads, due to which its application in drug delivery systems is increasing rapidly [111]. In addition to this, liposomes have gained importance as potential drug delivery systems owing to their stable lipid bilayer membrane, minimized enzymatic degradation and biocompatibility, and cell-specific targeting [112]. Further, liposomes can deliver the therapeutics at the target site following inhalation delivery thereby increasing therapeutic concentration, decreasing dose and dose frequency, and side effects. Thus, liposomal drug delivery *via* inhalation can reduce systemic side effects, improve patient compliance, and reduce the cost of therapy.

In view of this, Vyas et al., fabricated dry powder liposomes loaded with rifampicin for the treatment of TB *via* inhalation. The surface-decorated liposomes with maleylated bovine serum albumin (alveolar macrophage-specific ligands) were fabricated by employing egg phosphatidylcholine and cholesterol, while dicetylphosphate was used to provide a negative charge on the surface of liposomes. The vesicle size of liposomes was observed to be 3.6 µm. The penetration efficiency of rifampicin-laden liposomes in the base of the lung was observed to be 1.8 times higher than plain rifampicin aerosol solution *in vitro*. The 3.5-fold higher lung localization index of rifampicin was seen with surface-decorated liposomes than with non-decorated aerosolized liposomes. They observed significant distribution and retention of rifampicin in the lung from surface-decorated aerosolized liposomes than non-decorated aerosolized liposomes *in vivo* in albino rats. Thus, the authors concluded that the increased accumulation and retention of rifampicin in the lung is attributed to the presence of a targeting

ligand on the surface of liposomes [113]. In another interesting study, Patil and the team explored liposomes loaded with rifampicin for inhalational delivery to target TB. The liposomes were prepared using soya lecithin and cholesterol. The particle size of rifampicin-laden liposomes was found to be 6.4 µm. They observed substantially higher and extended release of rifampicin from the liposomes at pH 5.2 (simulated lung pH) when compared to the intestinal pH (pH 7.4) upon 10 h [114]. Peng et al., explored the potential of chitosan-coated liposomes laden with oxymatrine against RSV infection in mice *via* inhalation. These liposomes were comprised of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DSPG) and hydrogenated soybean phosphatidylcholine (HSPC) and displayed a vesicle size of 337 nm. The mucus penetration study using an *in vitro* two-layer model composed of the upper layer of mucin and sublayer of gelatin demonstrated higher (about 100%) penetration of oxymatrine from liposomes when compared to free oxymatrine. Significantly improved distribution and retention of oxymatrine was noticed in the lung owing to the chitosan coating. Moreover, three RSV-infected mice survived following intratracheal administration of chitosan-coated liposomes at a dose of 5 mg/kg. On the other hand, only two RSV-infected mice survived after treatment with free oxymatrine at a dose of 5 mg/kg [115]. Moreover, Yu and co-workers investigated the promise of inhalable liposomes co-loaded with ciprofloxacin and colistin against multi-drug resistance lung infections caused by *P. aeruginosa*. These liposomes were comprised of HSPC, DSPG, cholesterol, and polyethylene glycol. The optimized freeze-dried liposomes displayed a particle size of 166 nm. The liposomes demonstrated superior antimicrobial activity (lower minimum inhibitory concentration; MIC) against *P. aeruginosa* [116].

6.1.2. Niosomes

Niosomes are colloidal nanocarriers (NCs) that are bilayered structures (unilamellar or multilamellar vesicles) composed of lipid and non-ionic surfactants incorporated in the aqueous phase. Lipid components mostly include cholesterol or L-α-soya phosphatidylcholine which imparts stability to niosomes in biological fluids [117]. Whereas non-ionic surfactant spans and Brij are widely used, due to which niosomes are also referred to as “non-ionic surfactant vesicles” [118]. Recently, various ionic amphiphiles such as diacetyl phosphate, sodium deoxycholate, stearyl amine, etc. have also been used to augment the stability of vesicular suspension by inducing negative or positive charge. The size of niosomes ranges between 10 to 1000 nm and are preferred as drug delivery vehicles over liposomes due to their more chemical

stability and low cost [119]. These NCs are amphiphilic and can encapsulate the hydrophilic drug in the core region and the lipophilic drug in the non-polar region of the bilayer membrane [119]. These NCs can be functionalized to obtain the desired physicochemical properties and for the targeted delivery of drugs. In addition, the functionalization of niosomes delivered *via* the inhalation route allows improved drug delivery in the lower respiratory tract, with increased pulmonary exposure and minimized pulmonary absorption, resulting in a lower fraction of the drug reaching the systemic circulation. Niosomes also offer the controlled release of a drug resulting in sustained activity, reduced systemic exposure and normal cell toxicity, modification in the distribution profile of drugs, and increased accumulation of the encapsulated drug in the lung [118-120]. Thus, niosomes are reported to be a promising avenue in IBDD to treat PIs. By considering the above-mentioned benefits, Moazeni and the team developed inhalable niosomes for the delivery of ciprofloxacin to treat lung infections caused by *P. aeruginosa*. These niosomes were made up of cholesterol, tween 60, and span 80. The mean volume diameters of niosomes were observed between 4-8.5 µm. The niosomes demonstrated significant anti-microbial activity (lower MIC) than free ciprofloxacin against *P. aeruginosa* [120].

6.1.3. Solid lipid NPs (SLNPs) and nanostructured-lipid carriers (NLCs)

SLNs are composed of a biodegradable solid lipid matrix and a surfactant layer that are spherical with a mean size of 40-1000 nm [121-122]. NLCs are second-generation SLNPs that are comprised of solid and liquid lipids. Lipids used in their formation include triglycerides, sterols, fatty acids, and waxes whereas the surfactants include bile salts, lecithin, and copolymers [121]. Both sorts of NPs offer good stability and ease of aerosolization into droplets having apt aerodynamic diameters that contribute to their deep deposition to particular lung regions. These NPs cause significant accumulation and retention in the lung resulting from their improved adhesion to mucosal surface owing to their nanosize [123]. Further, these NPs are free from any organic solvents and therefore considered as more safe for inhalation use. Ease of scalability and biocompatibility are other chief benefits of these SLNPs and NLCs.

Due to the various advantages of these NPs in the IBDD, Varshosaz et al., fabricated SLNPs loaded with amikacin against cystic fibrosis lung infection and investigated their biodistribution potential in the lung following administration *via* inhalation route *in vivo* in the Wistar rats. The pulmonary administration of amikacin-laden SLNPs exhibited significant accumulation of amikacin in the lung and low accumulation in the kidney at 100 µL dose. In contrast, the

opposite findings were observed with intravenous administration of SLNPs at the same dose. Thus, from these findings, author concluded lowered renal toxicity and enhanced patient compliance upon pulmonary administration of SLNPs [124]. In another intriguing research, Almurshedi and colleagues developed ciprofloxacin-loaded NLCs for inhalation delivery to treat non-cystic fibrosis fronchiectasis. Stearic acid and oleic acid were employed as solid and liquid lipids, respectively to fabricate NLCs. This ciprofloxacin-loaded NLC displayed a particle size of 102 nm. The NLCs demonstrated a controlled release of ciprofloxacin for 8 h than free ciprofloxacin which exhibited more than 95% release within 4 h in PBS pH 7.4. They observed the remarkable antimicrobial activity of spray-dried NLCs loaded with ciprofloxacin against *P. Aeruginosa* [125]. Pardeike and team designed inhalable NLCs comprised of precirol ATO 5 and oleic acid for the delivery of itraconazole to treat invasive pulmonary aspergillosis. They found the sustained release of itraconazole from NLCs up to 4 h [126].

6.1.4. Nanoemulsion

Nanoemulsion is a heterogeneous colloidal system comprised of oil and aqueous phases with surfactant. The delivery of nanoemulsion *via* inhalation is reported to be more remarkable than the formulations including liposomes, micelles, suspensions, etc [127]. The noteworthy features of this system are significant kinetic stability and cargo bioavailability through increased mucosal penetration owing to their nanosize [128]. Reportedly, high encapsulation efficiency, controlled cargo release, and improved performance in IBDD are other key advantages of nanoemulsion [129]. Regardless of the benefits of nanoemulsion outlined above, many systems are disrupted upon dilutions with water which results in drug precipitation and uncontrolled absorption. Before nebulization, aqueous dilution with saline is necessary to regulate the formulations' tonicity and minimize aerosol-induced cough [130]. In view of this, Shah et al., fabricated inhalable plain nanoemulsion and chitosan-coated nanoemulsion of rifampicin for the treatment of TB. The nanoemulsion was prepared utilizing oleic acid and tween 80. The particle size of the nanoemulsion was noticed in the range of 43-59 nm. The nanoemulsion coated with chitosan exhibited a controlled release of rifampicin for 28 h when compared to the non-coated nanoemulsion. They noticed substantially higher (>95%) aerosol output and >75% inhalation efficiency of nanoemulsion. Additionally, *in vivo* pharmacokinetic study in Sprague-Dawley (SD) rats displayed lower plasma concentration of rifampicin from chitosan-coated nanoemulsion following administration at lung using a microsprayer aerosolizer in a dose of 2

mg/kg. These obtained pharmacokinetic study outcomes signify considerable deposition of nanoemulsion in the lung [127].

6.2. Polymeric NCs

Polymeric NCs showed promise in IBDD to treat a variety of PIs. These NCs are self-assembled structures formed from biodegradable or biocompatible amphiphilic molecules either natural or synthetic (ionic or non-ionic) that act as a stabilizing agent as well. During the self-assembly process, these nanoparticles encapsulate the drug molecules within the core or at the surface of the polymeric core based on their affinity [132]. Both natural and synthetic polymers are used in the IBDD. The sorts of polymers including Poly(lactide-co-glycolide) (PLGA), Polylactide (PLA), Poly-caprolactone (PCL), Hydroxyl propyl methyl cellulose (HPMC), etc have been employed to fabricate polymeric NPs for inhalation delivery to treat PIs [133]. These polymers are used as a carrier or excipients for IBDD which promotes apt aerodynamic features and evade particle aggregation thereby increasing particle dispersion and deposition in the lung [134]. Moreover, these NPs improve loading and control the release of cargo. Furthermore, the surface decoration (PEGylation) of polymeric NPs can enhance particle diffusion across the bacterial biofilm and localization at the target region of the lung [135]. In addition, surface decoration using chitosan has also been reported to enhance mucus penetration and deep lung deposition of NPs [134-135]. For instance, Cresti and team targeted cystic fibrosis through inhalable PEG-coated PLGA NPs loaded with peptide SET-M33. PEG-coated NPs demonstrated reduced mucoadhesion than non-coated PLGA NPs. Reportedly, the PEG-coated PLGA NPs demonstrated controlled release of peptide over 7 days. The anti-biofilm activity of these NPs was substantially higher against *P. aeruginosa* after 72 h [135]. In another intriguing research, Shah et al., were assessed the potential of PLGA NPs laden with linezolid against TB *via* inhalation. They employed plasdone and α-phosphatidylcholine as stabilizers in the fabrication of PLGA NPs. These NPs exhibited particle size in the range of 143-178 nm. The optimized PLGA NPs demonstrated prolonged release of linezolid for 120 h. *In vitro* lung deposition study using a cascade impactor displayed mass median aerodynamic diameter (MMAD) of 3.8 µm signifying the possibility of deep lung deposition of NPs. Additionally, a potent antimicrobial effect (lower MIC) was observed with NPs against *M. tuberculosis* [136].

6.3. Micelles

Micelles are nanoscopic supramolecular structures formed from biocompatible and biodegradable amphiphilic block copolymers, which above critical micelle concentration in water self-assemble in spherical micellar form [137]. The size of these NPs ranges between 10 to 100 nm which offers an increase in bioavailability and penetration of drugs and makes micelles particularly applicable for the inhalation delivery of drugs that need to reach systemic circulation [138]. However, micelles can also be formulated to specifically increase the residence time of the drugs in the lungs and therefore maximize the ratio between lung exposure and systemic exposure, to minimize adverse effects [57]. In addition to this, micelles offer good stability due to low CMC value (0.1-1 μM), controlled drug release, ease of functionalization, minimized side effects, stimuli-sensitivity, high surface-to-volume ratio, low production cost, and target selectivity [139]. The presence of a hydrophilic shell of micelles protects the system from alveolar macrophage uptake that enhances lung exposure of cargo thereby reducing the dose frequency and enhancing patient compliance [140].

By keeping the potential of micelles in IBDD in mind, Estefanía and co-workers developed inhalable micelles loaded with rifampicin to treat TB. The micelles were developed using soluplus copolymers and the particle size of these freeze-dried micelles containing rifampicin was found to be 90 nm. These micelles displayed sustained release of rifampicin for more than 72 h in PBS pH 7.4. In addition, MMAD of freeze-dried micelles was 3.9 μm revealing their potential for deep lung deposition. The inhalable micelles also exhibited a more significant antibacterial effect (MIC: 1 μg/mL) than plain rifampicin (MIC: 5 μg/mL). Furthermore, the *in vivo* biodistribution study in SD rats disclosed a 100-fold higher accumulation of rifampicin following pulmonary (surgical puncture tracheotomy) administration of micelles at a dose of 0.3 mg micelles per rat [141]. In another interesting study, Galdopórpora et al., designed soluplus-based mannosylated nanomicelles loaded with rifampicin and curcumin for inhalable delivery to treat TB. These nanomicelles disclosed a particle size of 162 nm. The MMAD of nanomicelles was less than 3 μm confirming their likelihood for deep lung deposition. The release of both drugs was noticed to be sustained from mannosylated nanomicelles than non-mannosylated nanomicelles. Compared to non-mannosylated nanomicelles, mannosylated nanomicelles showed substantial (2-fold decrease in mycobacterial colony forming unit) antibacterial efficacy against *M. tuberculosis*. Further, the maximum accumulation of drugs was seen in the lung from

mannosylated nanomicelles than non-mannosylated nanomicelles upon intratracheal administration of 3 mg/mL micelles in SD rats. This increased deposition could be due to the active targeting of nanomicelles towards alveolar macrophages containing overexpressed mannose receptors [142].

6.4. Nanocrystals

Nanocrystals are nanosized range carrier-free colloidal delivery systems. These are nanoscopic crystals composed of 100% parent compounds that are stabilized with surfactants or polymeric steric stabilizers [143]. In comparison to other carrier-based nanoparticles, nanocrystals are advantageous in drug loading (50-90% w/w) and stability [144]. Rod shape of nanocrystals contributes to the enhancement of penetration of drugs through mucus membrane than spherical-shaped NPs [145]. In addition, nanocrystals can be chemically modified for the controlled release of antidiabetic drugs to minimize side effects and enhance their therapeutic efficacy for prolonged periods [146-150]. Reportedly, nanocrystals can improve lung deposition of loaded therapeutics *via* minimization of macrophage clearance [145]. In view of this, Sabuz et al., developed ciprofloxacin-loaded poly(2-ethyl-2-oxazoline) inhalable nanocrystal to treat lower respiratory tract infections. This nanocrystal displayed controlled cargo release for an extended period. From the aerodynamic characteristics, authors concluded that nanocrystals would deposit deep in the lung [147].

6.5. Hybrid lipid- polymer (HLP) NPs

HLP NPs have emerged to overcome the limitations associated with single polymeric or lipidic NPs. The limitations like drug leakage and structural damage can be resolved through the fabrication of HPL NPs. In these NPs, a core-shell structure is composed of polymeric which is coated by a phospholipid layer. The phospholipid (highly biocompatible) layer improves cargo retention inside the polymeric core. HLP NPs confer various benefits including biocompatibility, significant structural integrity, and capacity to load hydrophilic and hydrophobic therapeutics, controlled release, targeting potential, and stability [151]. Further, these NPs are capable of improving the delivery and performance of therapeutics administered *via* inhalation route by overcoming various biological and other barriers related to the respiratory tract. Thus, this approach can have the potential to deliver various drugs *via* inhalation route to treat PIs efficiently.

By keeping the potentials of HLP NPs in inhalational drug delivery, Kaur and team designed surface-active HLP NPs laden with voriconazole to treat pulmonary aspergillosis with improved lung deposition and retention after nebulization. They used dipalmitoylphosphatidylcholine (DPPC) as a lung-specific phospholipid and chitosan as a polymer. These HLP NPs disclosed particle size between 228-255 nm. The complete *in vitro* release of voriconazole was observed from plain voriconazole suspension within 4 h. On the other hand, the release of voriconazole was observed to be sustained for more than 48 h from the HLP NPs. Additionally, the HLP NPs displayed better lung pharmacokinetics (C_{max}: 26.3 µg/mL and AUC_{0-24}: 178 µg/mL.h) than plasma pharmacokinetics (C_{max}: 7.8 µg/mL and AUC_{0-24}: 69 µg/mL.h). The presence of DPPC increased the diffusion of NPs into the lung by minimizing their uptake by macrophages. On the other hand, chitosan improved the mucoadhesion of NPs which resulted in enhanced retention of drugs in the lung [152].

6.6. Metallic NCs

NCs such as metallic nanoparticles have also shown their potential in drug delivery applications to treat pulmonary infectious diseases and their associated comorbidities [153-154]. Gold and silver nanoparticles as non-invasive drug carriers have been extensively used for targeting drugs to their site of action [155]. Over the past few years, their unique colours, anti-microbial properties, tunable surface Plasmon resonance, or typical electronic properties led to their use in biomedical applications [154]. Further, their chemical inertness and minimum toxicity make them suitable agents for drug delivery purposes [154]. Remarkably their ease of synthesis of various shapes i.e., spherical, rod, cage, etc., and sizes ranging from 1 nm to more than 100 nm are responsible for their peak interest. In addition, these can be easily functionalized with a variety of biomolecules and targeting ligands owing to their negative charge [156]. Keeping this in mind, Nadworny and the team designed a nebulized nanosilver solution to treat respiratory tract infections. They noticed significant ($p<0.005$) antimicrobial efficacy against *P. aeruginosa*, *S. aureus*, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections [157].

7. Inhalable vaccines and nano vaccines for PIs

Despite the development of vaccination, the recurrence of infectious and non-infectious diseases remains a challenge worldwide. The mucosal membrane is one of the chief infection sites for most of the pathogens causing PIs [158]. Thus, the mucosa of the respiratory tract serves as the first line of defense against the invasion of respiratory pathogens in the human body [159]. The

mucosal vaccines have the potential to stimulate mucosal immunity causing secretion of immunoglobin A (IgA) antibody which aids in the trapping and removal of harmful microbes or antigens from the mucus [160]. Thus, these inhalable vaccines can minimize the risk of PIs including COVID-19 by preventing the entry of pathogens through mucosal site [161].

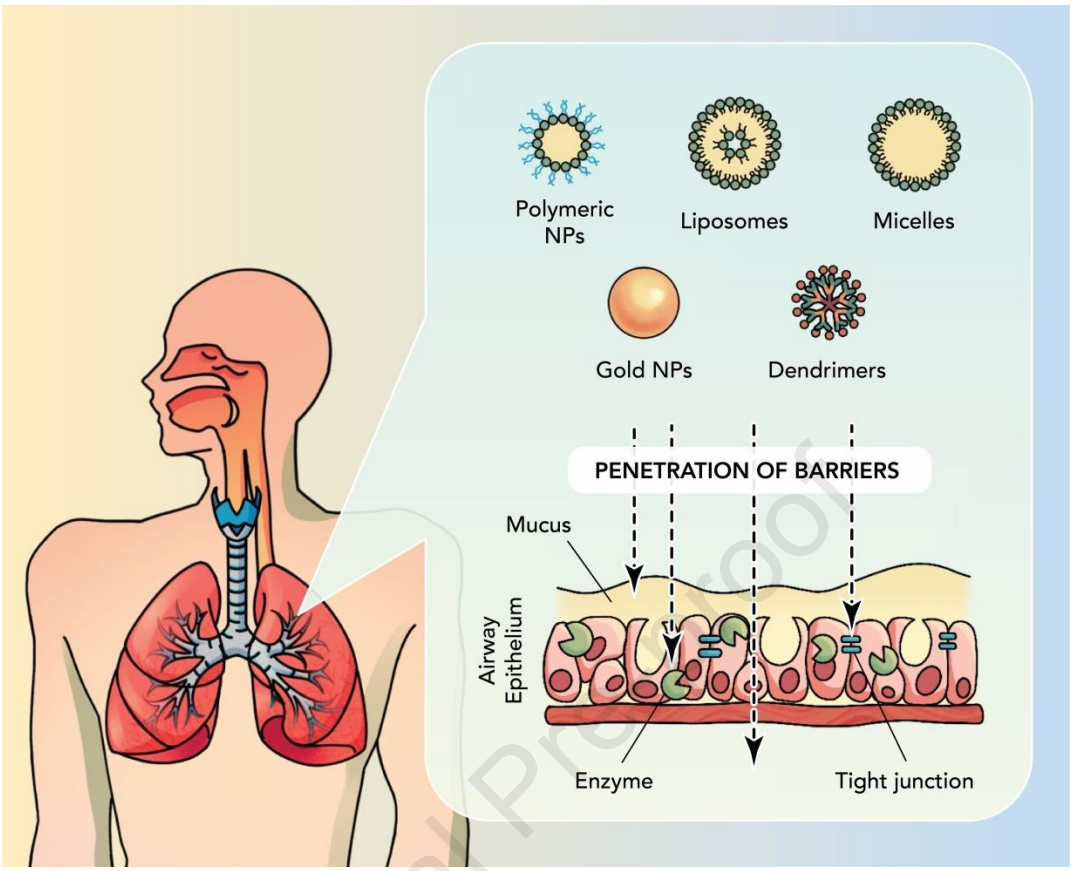
Although needle-based vaccination has commonly been used for the prevention and treatment of PIs, it still holds numerous challenges and limitations**.** This type of vaccination primarily induces systemic immune responses, which are non-specifically directed at the affected site of infection such as mucosal areas [162]. Notably, injectable vaccines require specific storage conditions as they are either formulated as unstable solutions or lyophilized powders that require storage in cold conditions or need reconstitution, respectively. Not only this but these vaccines can be only administered by healthcare workers or clinicians, which can be a major drawback in non-industrialized countries or remote areas [163]. These limitations and challenges with needle-based vaccination highlight an urgent need for an alternative way of vaccine platforms that can outweigh the above-mentioned limitations or challenges.

Inhalable vaccination is a promising strategy that showed great promise in the prevention of different kinds of PIs by overcoming the aforesaid limitations. The chief benefits of inhalable vaccinations are non-invasive, simple administration, the capability of mass immunization, and better patient compliance when compared to needle-based vaccination [164]. Further, the stability problems allied with the delivery of vaccines in liquid form can be resolved using their delivery in dry form through DPI. Vaccines in dry form may abolish the need for cold chain storage and provide a longer vaccine shelf-life. The manufacturing of vaccines in dry powder form without compromising stability has been reported to be successful using techniques like microwave vacuum drying and fluid air polar dry spray drying [165-166]. In addition, the key benefits of spray drying over other drying techniques are their ability to tailor the physicochemical and solid-state attributes of DPI formulations to provide aerodynamic qualities appropriate for deep lung deposition [167]. Notably, drying vaccines using quality by design (QbD) is a new approach that helps manage critical material and process parameters, producing vaccines with the essential critical quality attributes [165-166].

Inhalable vaccination induces both mucosal and systemic immunity. The primary line of defense towards microbial invasion is generated by inhalable vaccinations, which may provoke an immune response at the mucosal site. This mucosal immunity is brought on by effector T cell

proliferation, which results in the generation of immunoglobulin (Ig)G and IgA antibodies, effectively preventing microbial infection and transmission [168]. Moreover, the systemic immunity induced by the inhalable vaccines through the generation of systemic neutralizing antibodies and IgA in the lung and nasal compartments [169]. However, certain barriers associated with inhalable vaccinations are mucus, tight junction of epithelium, enzymes, etc. The uptake of vaccines in immune cells (dendritic cells) is another significant challenge. Further, the control of the size and shape of particles of vaccine formulations is of huge importance to achieve better uptake and significant immunostimulation. The vaccine formulations containing a size between 200-300 nm and spherical shape displayed considerable uptake by antigen-presenting (dendritic) cells [170-171].

The above-mentioned challenges in the path of inhalable vaccinations can be conquered *via* nanotechnology. The sorts of nanoparticulate approaches showed improved uptake of vaccines and immune activation through control of their particle size and shape. Various nanoparticulate approaches such as polymeric NPs, liposomes, micelles, and dendrimers have been used in the delivery of inhalable vaccinations to achieve better immunization [172] (Fig. 5). These nanoparticulate-based vaccines following inhalation are uptaken by dendritic cells causing induction of cytokines expression and T-cell mediated response. Further, β-cells will be provoked which results in the secretion of IgA and IgG antibodies that provide immunity against pulmonary infections caused by pathogens [159]. The mechanism of induction of immune response following inhalable vaccination is depicted in Fig. 6.



724

725 **Fig. 5:** Nanoparticulate approaches in delivery of inhalable vaccines to improve immunization

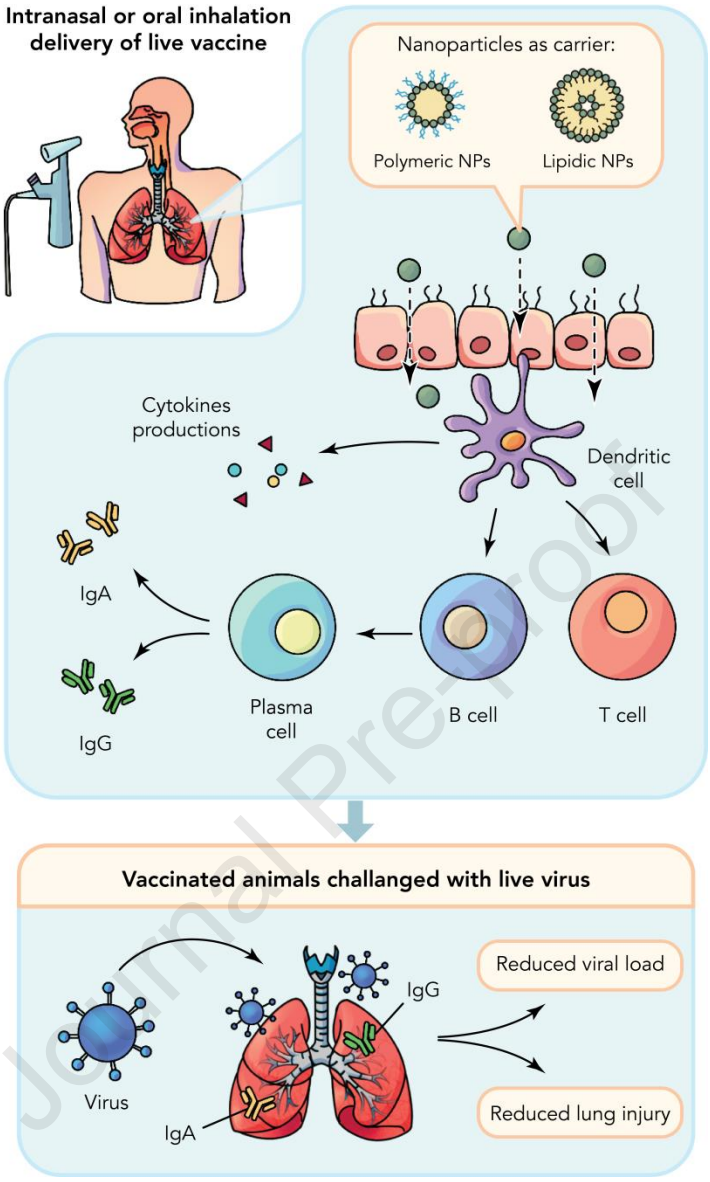


Fig. 6: The mechanism of induction of immune response by inhalable vaccines

Given this, Zhuo et al., fabricated chitosan-based inhalable nanovaccines containing spike protein of SARS CoV-2 for protection against SARS CoV-2 infection. These vaccines stimulated lung mucosal immunity *via* the generation of spike-specific antibodies which can protect the host from SARS CoV-2 infection devoid of any systemic toxicity. They noticed significant secretion of IgA with inhalable vaccines suggesting better protection from SARS CoV-2 at the mucosal site. Additionally, substantial stimulation of dendritic cells was observed in the mice following inhalable vaccination indicating better protection from SARS CoV-2 [173]. In another interesting study, Zeng and team developed inhalable nanovaccines comprised of synthetic ds-RNA (poly-

I:C) as an immune adjuvant and biomimetic pulmonary surfactant liposomes which acts as virus capsid and the receptor binding domains against SARS-CoV-2 infection. Substantially high titer of IgA was noticed in the respiratory tract secretion following inhalable vaccination than subcutaneous vaccination. Thus, they concluded significant mucosal immunostimulation and protection from SARS CoV-2 with inhalable vaccination than subcutaneous vaccination [174]. Furthermore, Wu and co-workers designed an inhalable DNA vaccine against *M. tuberculosis* using mannosylated chitosan with the intent of enhancing uptake into dendritic cells containing expressed mannose receptors. This vaccine demonstrated significant uptake and provoke of immune response in the mice *in vivo* [175].

Several vaccines used to treat PIs *via* pulmonary routes are undergoing clinical trials at different phases. The Ad5Ag85 vaccine is an adenovirus-based vaccine for TB administered by aerosol undergoing phase 1 trials. This interventional study used 36 participants [NCT02337270]. Similarly, ChadOx1 85A vaccines undergo early phase 1 clinical trials to assess the safety and immunogenicity potential of the vaccine against TB following inhalation. In this study, the immunogenicity potential of the inhalable vaccine is determined in comparison with its intravenous administration. This interventional study used 39 participants [NCT04121494].

8. Inhalation devices and challenges

Inhalation therapy is the cornerstone to managing diverse pulmonary infections. Therefore, using an apt inhalation technique is highly required for treating pulmonary infections efficiently. However, in practice, patients continue to struggle with improper inhaler technique [176] and even experienced patients frequently mishandle their devices [177]. Errors in inhaler handling and non-adherence can impact drug delivery and reduce the benefits of treatment [178-179]. Notably, the misuse and poor adherence to inhalers may also increase the risk of hospitalization.

The sorts of inhalation devices employed in the inhalation drug delivery against PIs are dry powder inhalers (DPIs) [180-181], pressurized metered-dose inhalers (pMDIs) [182], soft-mist inhalers (SMI) [183-184], and nebulizers [185]. The powder formulation is aerosolized *via* a DPI device, which de-agglomerates or separates the drug particles from the carrier before delivering the dosage to the patient's deep lungs. DPIs are employed to inhale high doses of drugs from one to several tens of milligrams within seconds. DPIs are of three main types including single dose DPIs, multiple doses DPI, and power-assisted (active) DPIs [186]. Single-dose DPIs are chiefly influenced by the respiratory flow of the patients. These devices are breath-activated in which a

capsule is pierced into the device by needles set to pressure buttons. Multiple-dose DPIs are multi-dose and multi-unit DPI devices employed as an alternative to single-dose DPIs [187]. Different hydrophobic drugs can be delivered through DPIs proficiently. Additionally, the solid-state formulations delivered *via* DPIs have long-term storage stability. The majority of DPI-based formulations are made up of combinations of drugs or drugs' excipients (non-respirable carriers). The non-respirable carriers such as glucose, sucrose, mannitol, sorbitol, xylitol, and raffinose have been used in the DPI formulation in addition to the FDA-approved excipient lactose [188]. However, deprived inhalation in various pulmonary infections makes it difficult to achieve the significant lung deposition and therapeutic effect of the drug *via* DPIs. Power-assisted DPI devices have been created to address the problem associated with poor inhalation and they can be turned on at modest flow rates resulting in improved lung deposition [189]. Tiny size, economic, conveyable, low maintenance, and least environmental contamination than nebulizers are the important benefits of DPIs [190-191].

The pMDI is the commonly used moveable outpatient inhalation. The pMDI releases a drug aerosol *via* a nozzle at a rate of more than 30 ms^{-1} propelled by propellants like chlorofluorocarbons and hydrofluoroalkanes. This device causes deposition of only a small fraction (10-20%) of the drug in the lung [191]. Moreover, about 50–80% of the drug aerosol that is emitted by the spray hits the oropharynx due to its high velocity and big particle size [192]. Another barrier to the use of the pMDI is hand-mouth synchronization.

The SMI is an inhaler without a propellant that assimilates microelectronic dosimetric systems. It possesses a high proportion of fine particle fraction, low velocity, longer-lasting endurance, and is easier than a pMDI [193-194]. The SMI was reported to show 2-3 times higher pulmonary deposition when compared to pMDI. However, a significant challenge with SMI is the difficulty in drug loading into the device [195].

Nebulizers are particularly important for diseases where patients are unable to achieve the required flow rate and high pulmonary doses are required. Nebulizers are of three different sorts depending on how the medication solution is converted into aerosol ultrasonic nebulizers, vibrating mesh nebulizers, and jet nebulizers [196]. Ultrasonic nebulizers are portable devices. As ultrasound heat is generated, therefore, these devices are not preferred for the delivery of heat-labile therapeutics like proteins. The vibrating mesh nebulizer is a novel device that has advantages like quick treatment times, little residual volume, and better aerosol distribution

[197]. The main obstacle is the price. The mesh nebulizers are ideal for bedridden patients unable to conduct active inhalation because they do not require specific inhalation methods [198]. This is a highly employed technique in clinical trials and can deliver the formulations like solutions and suspensions. However, the protracted administration process required for therapeutic dose delivery and feeble lung deposition is the chief drawbacks. Besides, nebulizers are suitable for the delivery of liquid formulations composed of both hydrophilic and hydrophobic therapeutics [199-200]. Furthermore, controlling the threat of the device and environmental contamination is also challenging [201].

9. Inhaled formulations marketed or undergoing clinical trials for pulmonary infectious diseases

Several Food and drug administration (FDA) approved NPs/microparticles-based pulmonary inhalation formulations are available in the market for imaging, diagnostics, and treatment of respiratory diseases and some are in clinical trials at various phases [202]. For instance, an amikacin-loaded inhalable liposomal formulation was approved under the name Arikayce® in 2018 to treat mycobacterium avium complex lung disease [203]. Similarly, FDA approved dry powder inhalation formulation containing tobramycin encapsulated in lipid nanoparticles (TOBI® or Podhaler®) is fabricated by Novartis, Basel, Switzerland, and is employed for the management of lung infection caused by *Pseudomonas aeruginosa* [203-204]. Furthermore, inhalable ciprofloxacin-loaded liposomal formulation is in phase 3 clinical trials. This interventional type of study consisted of 278 participants with the objective to ascertain the safety and effectiveness of inhalable liposomal formulation in the management of chronic lung infections caused by *Pseudomonas aeruginosa* [NCT01515007]. Various inhalable nanoformulations marketed and available in clinical trials are summarized in Table 2**.**

10. Conclusion and Future Perspectives

The mortality and global burden of the range of PIs including pneumonia, COVID-19, tuberculosis, cystic fibrosis, influenza, etc are noticed to be very high and this is expected to increase rapidly in the near future. Considering the above fact, there is a dire need to focus on apt treatment strategies. The conventional delivery of available therapeutics (antibiotics, anti-virals, and antifungals) and biologics in the market possessed kind of challenges like resistance, fatal side effects, poor *in vivo* stability and therapeutic performance, etc. Therefore, appropriate delivery of approved therapeutics *via* an apt delivery route is of utmost importance to treat PIs.

Inhalation-based drug delivery could be a significant approach in treating PIs as it can reduce various drawbacks in the path of conventional delivery of drugs. The delivery of biologics through the inhalation route minimizes the degradation caused following administration by other routes. Moreover, inhalation delivery can deliver the drug to the target region of the lung which minimizes the systemic and other toxicities like organ toxicity of the drug.

However, beneficial inhalational delivery also posed some challenges such as physiological barriers, enzymes, and biofilm formation on the lung surface. Importantly, the physicochemical properties of drugs including molecular size, shape, density, lipophilicity, solubility, and polar surface area also contribute to their deposition and residence in the lung region. These barriers are responsible for the failure of therapy by clearing the drug through different mechanisms without interactions with lung tissues. Therefore, it is crucial to control the size, shape, and density of medicines employed for inhalation. Special efforts including the use of nanoparticulate-based delivery are of vital importance to circumvent the challenges in the path of inhalation route. The inhalation delivery of drugs using suitable NPs or microparticles comprised of biocompatible materials with lung and controlled size range can contribute to the site-targeted deposition of cargo in the specific region of the lung. The various polymeric, lipidic, hybrid lipid polymer, and metal NPs can have the potential to deliver drugs *via* inhalation to treat PIs. Further, surface modifications of these NPs cause an augment in the residence time of NPs in a particular region of the lung. Despite lots of studies on the inhalable delivery of NPs loaded with drugs, more efforts are needed to achieve the stability and scalability of such type of formulations.

Vaccines have also shown promise in the treatment and prevention of PIs. However, needle-based vaccines possess issues related to the stability and requirements of healthcare practitioners. Inhalable vaccines or nano vaccines can serve as a substitute for needle-based vaccines which can solve the concerns and target various areas of the respiratory tract and pulmonary region. Extensive research is going on the inhalable vaccines and nanovaccines to achieve protection from diverse PIs. Different kinds of NPs also have shown promise in vaccine delivery by enhancing their performance. However, only several vaccines are undergoing clinical trials and additional efforts are required to increase these numbers.

The essential element of pulmonary drug delivery is the inhalation devices including DPIs, pMDIs, SMI, nebulizers, etc. The various factors that contribute to medication delivery using

inhalation devices include deprived inhalation in the patients who suffered with various PIs, poor drug loading into devices, environmental contamination, etc. Further, the choice of dry powder inhalation device is very crucial because diverse properties of dry powders including size, shape, surface charge, density, and moisture content affect their aerosolization. Therefore, further technological improvements are needed to overcome the above challenges and meet the patient's needs.

Although extensive research in inhalation delivery for infectious diseases, very few passed clinical trials and reached the market. The chief reasons behind the less marketed nanoparticulate-based inhalation formulation are stability, biocompatibility, safety-related concerns, complex fabrication processes, and non-affordability. Thus, additional efforts are essential to conquer the aforesaid challenges and reach more inhalation-based formulations to treat PIs in the market.

Credit authorship contribution statement

Popat Kumbhar: Concept building, writing original draft, review and editing; **Jaskiran Kaur:** Concept building, writing original draft, review and editing; **Gabriele De Rubis:** Review and editing; **Keshav Raj Paudel:** Review and editing; **Parteek Prasher:** Review and editing; **Vyoma Patel:** Review and editing; Leander **Corrie:** Review and editing; **Dinesh Kumar Chellappan:** Review and editing; **Gaurav Gupta:** Review and editing; **Sachin Kumar Singh:** Concept building, review and editing, total administration of project; **Vandana Patravale:** Concept building, review and editing, total administration of project; **John Disouza:** Concept building, review and editing, total administration of project; **Kamal Dua:** Concept building, review and editing, total administration of project.

Acknowledgements

The authors would like to acknowledge the support from their respective institutes throughout the review writing process.

Declarations of interest

The authors declare that they have no conflicts of interest with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Funding sources

No specific grant from funding agencies in the public, commercial, or not-for-profit sectors has been received for this work.

Data availability

No data was used for the research described in the article.

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1485 **Table 1.** *In vitro* and *in vivo* performance of several inhalable NPs used for treating PIs

Type of nanocarrier	Drug	Disease targeted	Performance		Reference
			In vitro	***In vivo***	
Liposomes	Rifampicin	Tuberculosis	• Substantial (about 3.5 fold) higher penetration of rifampicin from surface – decorated liposomes in the lung than surface non-decorated liposomes • Controlled and maximum release of rifampicin (83%) in simulated lung fluid than intestinal fluid (59%) after 10 h	• More than 62% of rifampicin accumulation in the lung tissues from surface -decorated liposomes than surface non-decorated liposomes *in vivo* in the Wistar rats	113
	Rifampicin	Tuberculosis	• No growth of *M. tuberculi* microorganisms was noticed with liposomal formulation containing rifampicin at 50 µg/mL and 100 50 µg/mL concentration than plain rifampicin	--	114
	Oxymatrine	Respiratory syncytial virus infection	• Complete (100%) penetration of liposomal oxymatrine through mucus than free oxymatrine within 12 h	• Substantially higher distribution of oxymatrine from coated liposomes than uncoated liposomes *in vivo* in the lung of BALB/c mice • Survival of 38% of RSV-infected mice after treatment with liposomes when compared to free oxymatrine (survival was 20%)	115
	Ciprofloxacin and colistin	Lung infections caused by *P. aeruginosa*	• Significant ($p<0.005$) antimicrobial effect against MDR *P. aeruginosa* by	--	116

			antibiotic co-loaded liposomes than free antibiotic solution		
Niosomes	Ciprofloxacin	Lung infections caused by *pneumoniae*, *S. pneumoniae*, and *P. aeruginosa*	• Significantly lowered MIC (12.5 µg/mL) than plain ciprofloxacin (50 µg/mL) against *P. aeruginosa*	--	120
Solid lipid NPs	Amikacin	Cystic fibrosis	--	• Significantly ($p<0.005$) enhanced accumulation of amikacin in the lung than other organs *in vivo* in male Wistar rats upon pulmonary administration of SLNPs when compared to its intravenous administration	124
NLCs	Ciprofloxacin	Non-cystic fibrosis fronchiectasis	• Controlled (only 48%) release of ciprofloxacin upon 8 h when compared to complete (98%) ciprofloxacin release from free ciprofloxacin solution within 4 h	--	125
	Itraconazole	Fungal infections	• About 95% of itraconazole release from NLCs within 4 h	--	126
Nanoemulsion and Chitosan-coated nanoemulsion	Rifampicin	Tuberculosis	• Controlled release (about 85%) of rifampicin from chitosan coated nanoemulsion than uncoated nanoemulsion within 24 h	• Lowered plasma concentration (5.4 µg/mL.h) upon inhalation administration in rats at a dose of 2 mg/kg	129
PLGA NPs and PEG-coated PLGA NPs	Peptide SET-M33	Cystic fibrosis	• Controlled release (about 85%) of peptide SET-M33 for 7 days • Significant anti-biofilm activity by coated NPs at 24 µM against *P. aeruginosa* than uncoated	--	135

			NPs after 72 h		
PLGA NPs	Linezolid	Tuberculosis	• Sustained release (89%) of linezolid for 120 h in simulated lung fluid	--	136
Micelles	Rifampicin	Tuberculosis	• Sustained release of rifampicin (about 50% release) within 72 h • 5-Fold lowered MIC of micelles than plain rifampicin against *M. tuberculosis*	• Improved (>95%) deposition of rifampicin in lung *in vivo* in SD rats after pulmonary administration	141
Mannosylated nanomicelles	Rifampicin and curcumin	Tuberculosis	• Controlled release of rifampicin (>80 %) from mannosylated nanomicelles than plain nanomicelles (100% release) after 24 h • 5-Fold lowered MIC of micelles than plain rifampicin against *M. tuberculosis*	• Significant (> 90%) deposition of drugs in lung and their retention in lung for more than 24 h in SD rats	142
Dried NP	Itraconazole	Invasive pulmonary aspergillosis	• 2.9 µm MMAD of optimized NPs disclosed their maximum deposition in lung	--	148
Hybrid lipid-polymer NPs	Voriconazole	Pulmonary Aspergillosis	• Controlled (only 70%) release of voriconazole after 48 h	• Enhanced lung AUC, T_{max} and MRT of voriconazole by 5, 4, and 3-fold, respectively in Balb/c mice than plasma pharmacokinetics	152

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1489 **Table 2.** Marketed and clinical trials undergoing formulations for PIs

Drug name	Type of nanoformulation	Formulation name	Infectious disease targeted	Status	Reference
Amikacin	Liposomes	Arikayce®	Lung disease caused by *Mycobacterium avium complex*	Approved	194
surfactant protein B and C	Liposomes	Curosurf®	Respiratory distress syndrome	Approved	194-195
Ciprofloxacin	Liposomes	Apulmiq	Noncystic fibrosis bronchiectasi	Approved	
Tobramycin	Lipid nanoparticles	TOBI® Podhaler®	Chronic pulmonary infections caused by *Pseudomonas aeruginosa*	Approved	192-193
Ciprofloxacin	Liposomes	--	Infections caused by *Pseudomonas aeruginosa*	Phase 3	NCT01515007
Ciprofloxacin	Liposomes	--	Non Cystic Fibrosis Bronchiectasis	Phase 3	NCT02104245
Ciprofloxacin	Lipid microparticles	--	Non-cystic fibrosis bronchiectasis	Phase 3	NCT01764841
Arikayce	Liposomes	--	Cystic Fibrosis	Phase 2	NCT00558844

Arikayce	Liposomes	--	Bronchiectasis and infections caused by *Pseudomonas*	Phase 2	NCT00775138
Hydroxychloroquine (TLC19)	Liposomal suspension	--	COVID-19	Phase 1	NCT04697654
Lactoferrin	Liposomes	--	COVID-19	Phase 2	NCT04475120

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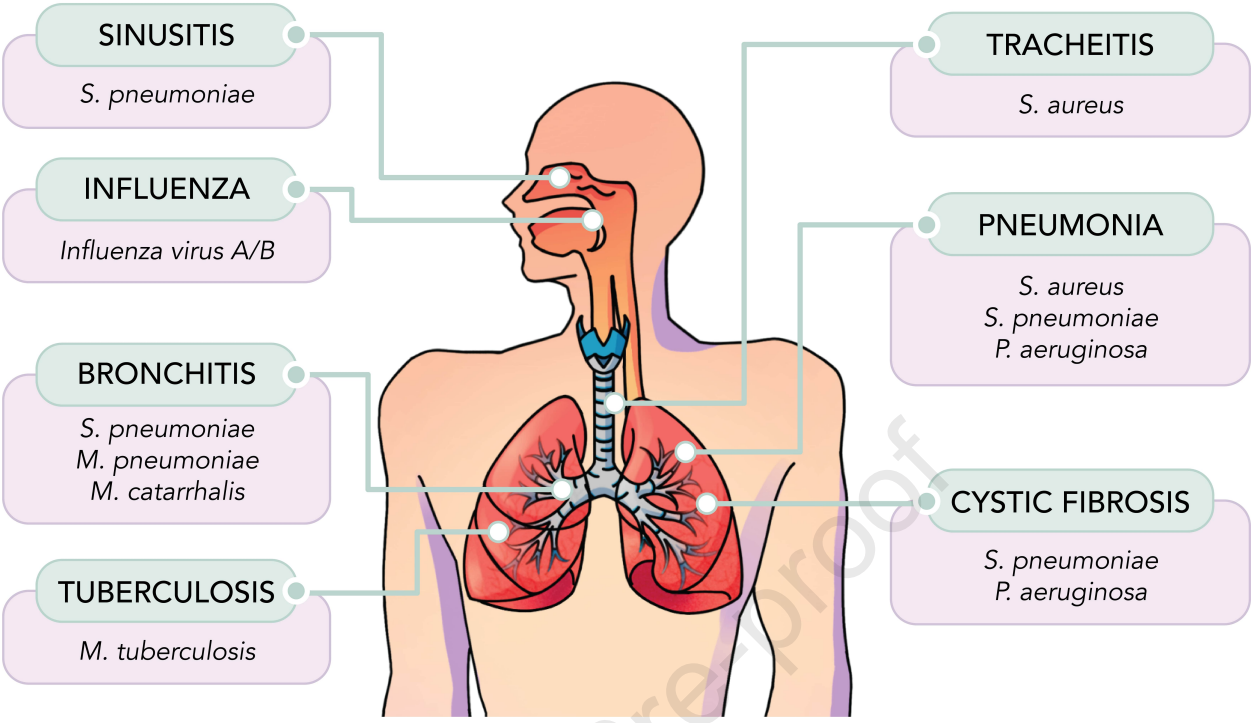

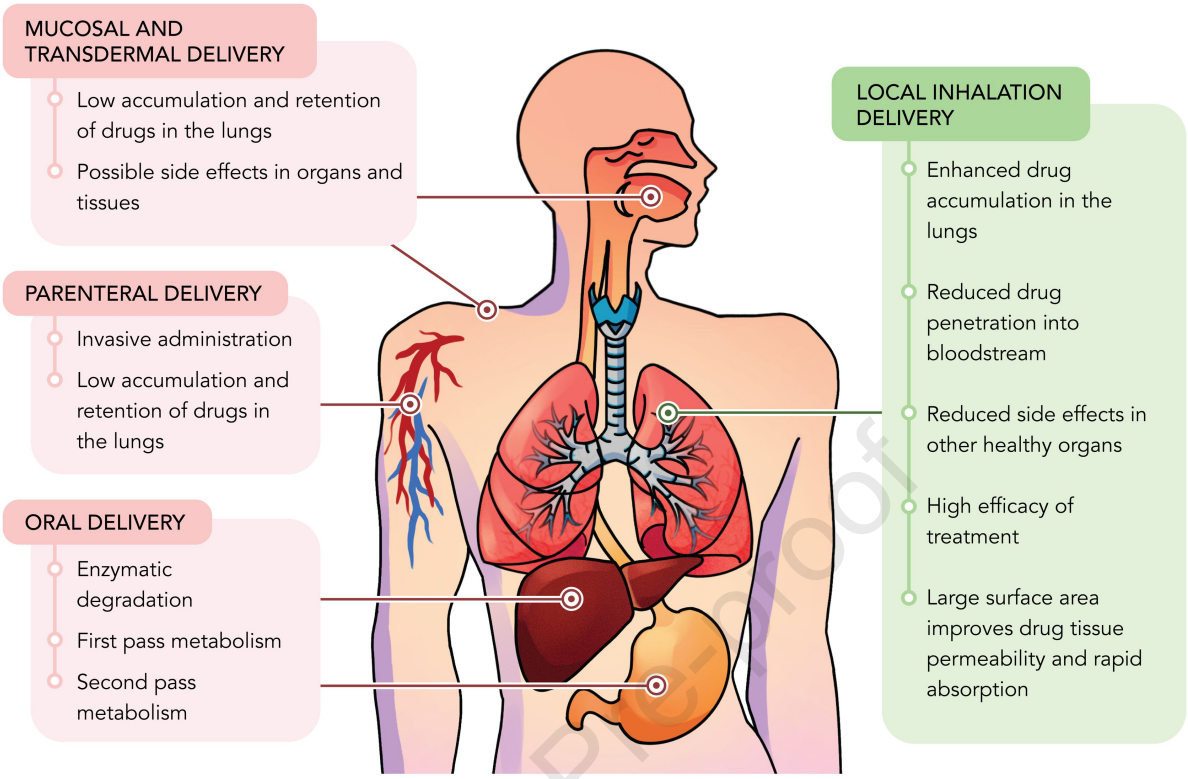

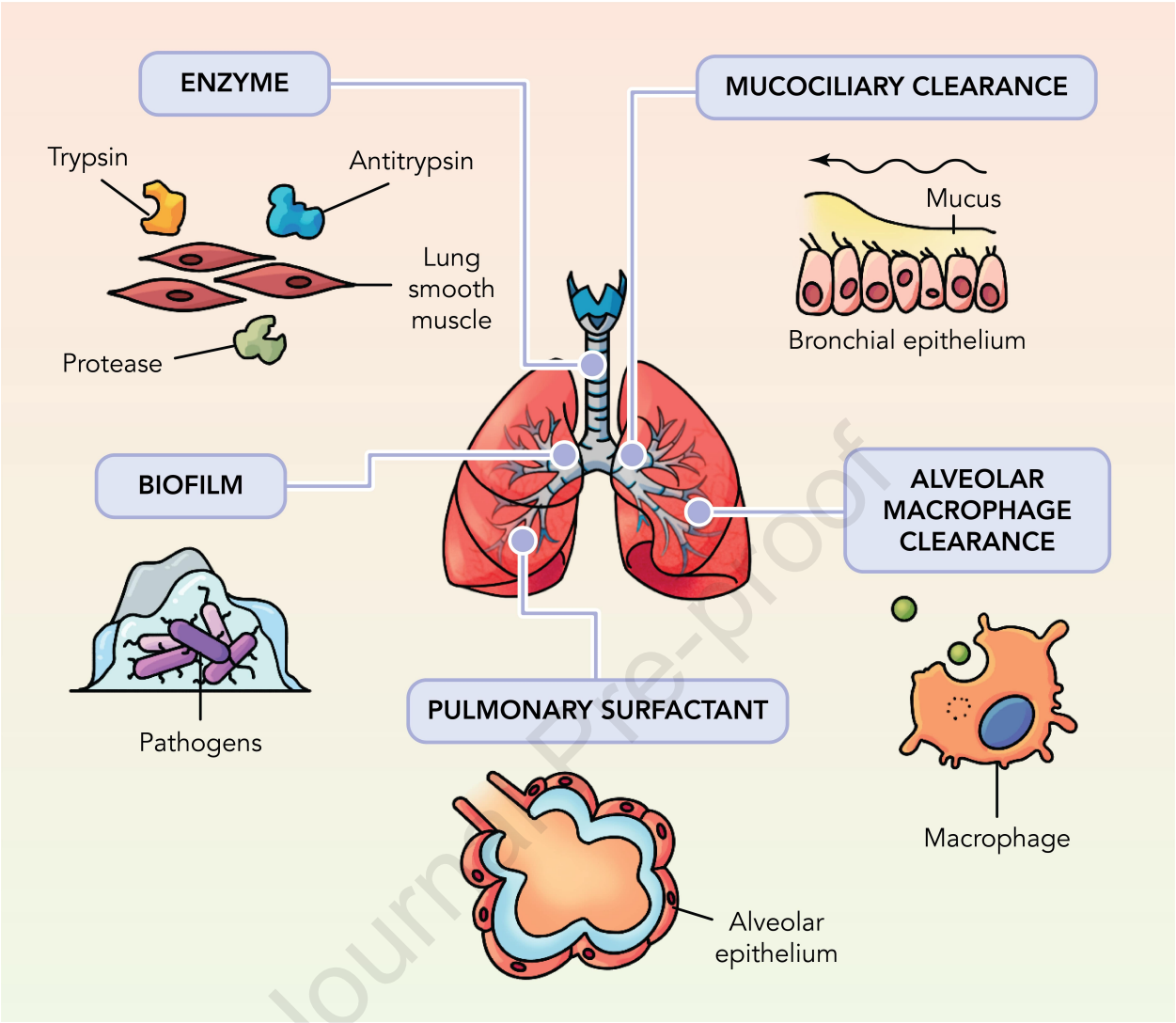

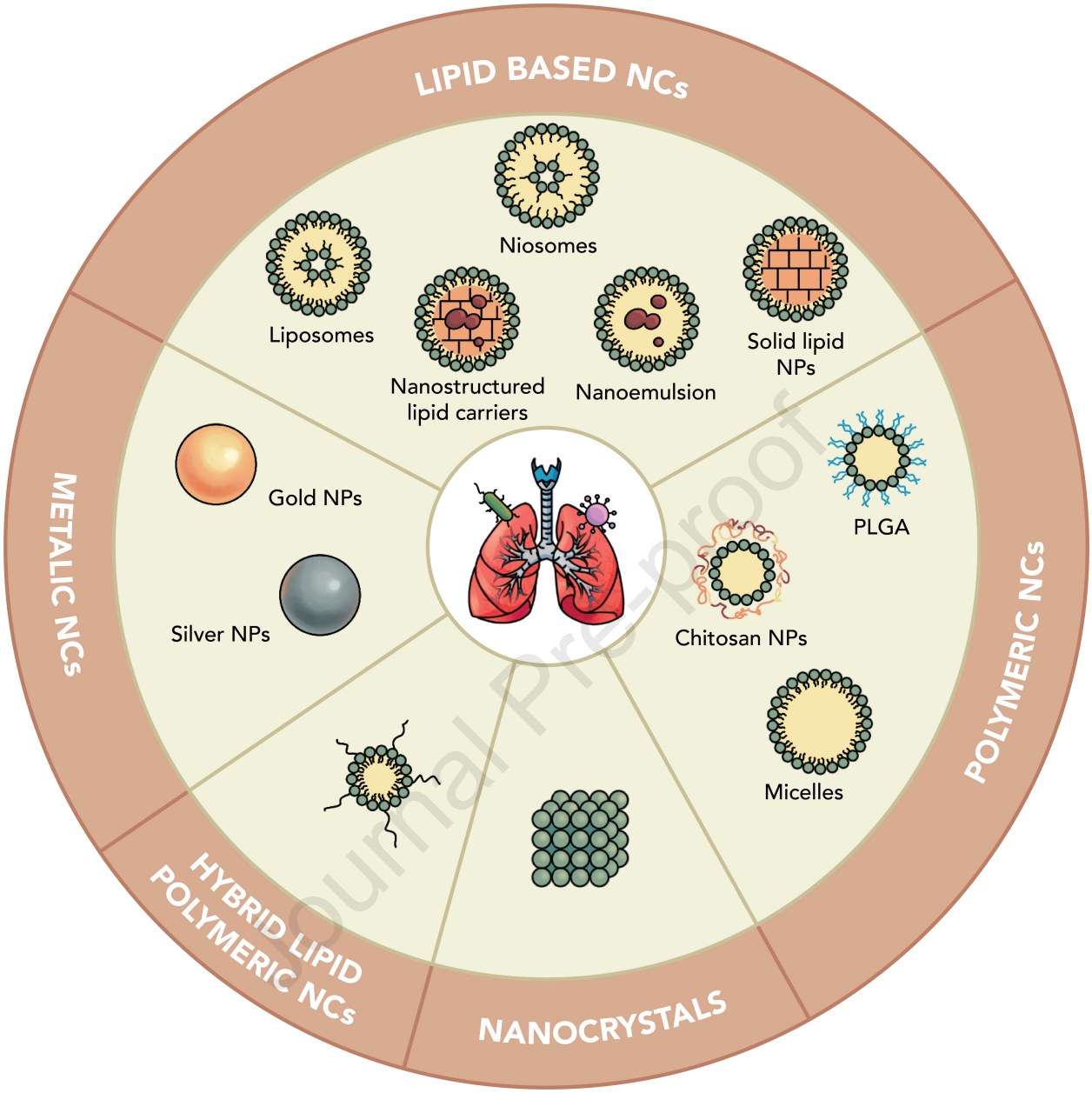

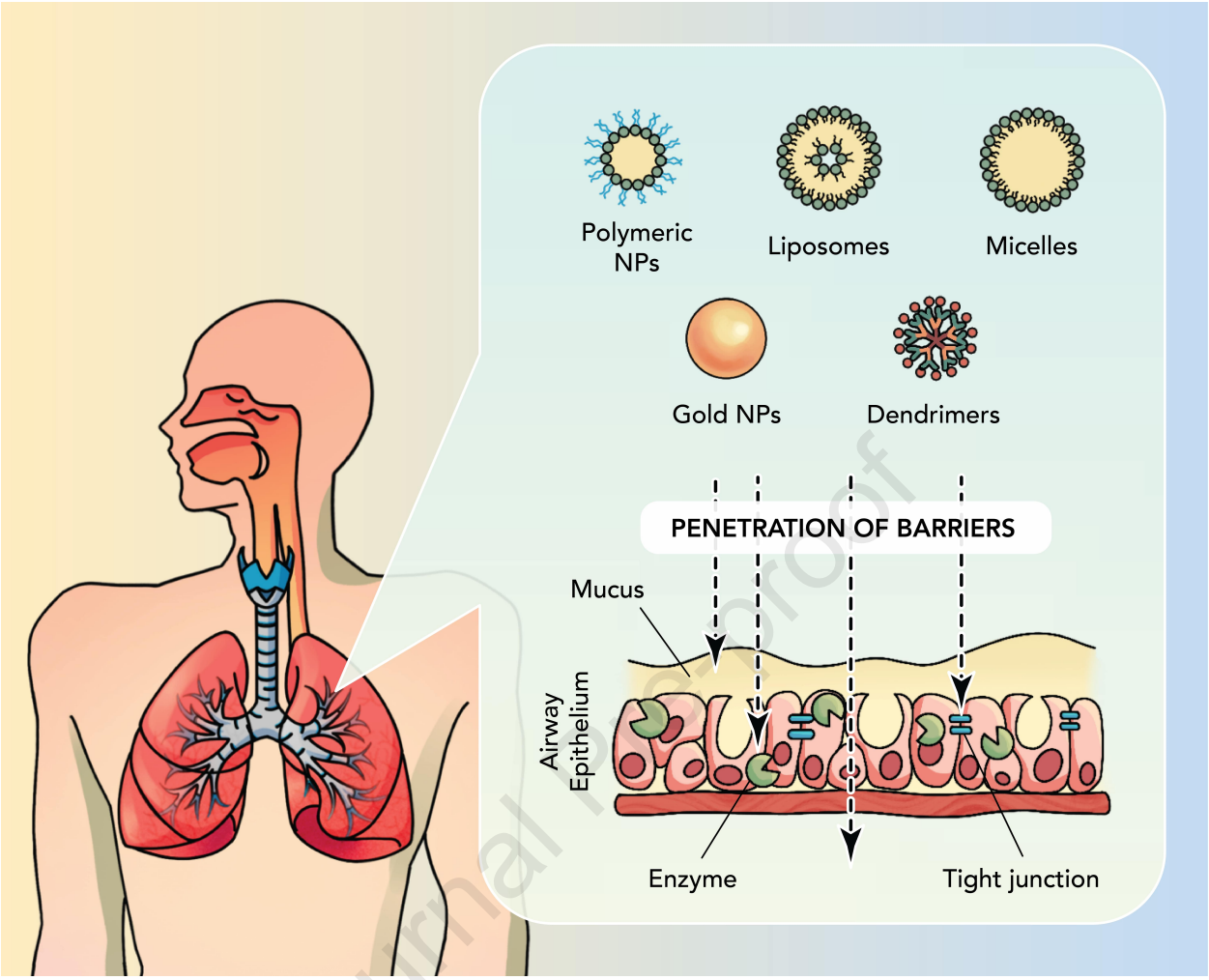

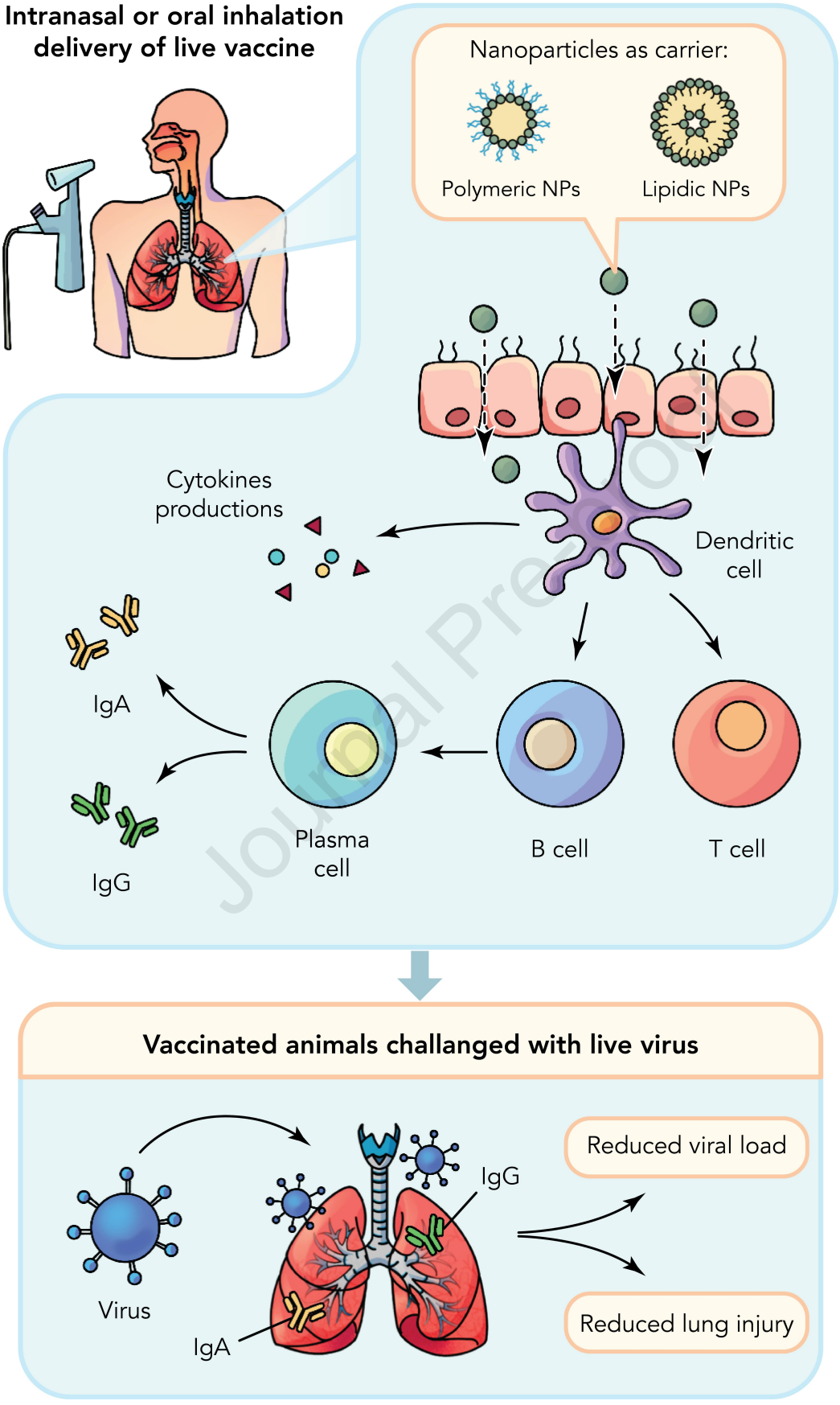

Highlights

- Pulmonary infections (PIs) are a key hazard to the public health system universally.
- Inhalation-based drug delivery has the potential to manage PIs efficiently.
- Nanoparticles assume an imperative role in inhalation drug delivery.
- Vaccines and nano vaccines can be promising to prevent and treat PIs.
- Inhalation devices are major contributor to success of therapy.

Declaration of interests

✓ ☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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