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Nano Science in Pulmonary Drug Delivery

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ABSTRACT

Respiratory diseases are a common disease with high incidence all over the world, pose a serious threat to human health and are considered to be an economic and social burden. The application of nanotechnology in drug delivery systems has created new treatments for respiratory diseases. In this regard, this review has systematically introduced the physicochemical properties of nanoparticles (NP). We have reviewed the current state of research on various Nano carriers in the treatment of respiratory diseases, including liposomes, solid lipid Nano carriers, and polymer Nano carriers. The application of nanotechnology overcomes some of the deficiencies inherent in drugs and offers endless possibilities for the development of drugs for the treatment of respiratory diseases. However, most of the relevant research is in the preclinical stage and the assessment of safety remains a difficult task. Future research is needed to focus on changes in the performance, molecular mechanisms, and potential toxicity of therapeutic Nano medicines.

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Abbreviations

DCs:	Dendritic cells
DOX:	Doxorubicin
DPPC:	Dipalmitoylphosphatidylcholine
FDA:	Food and Drug Administration
LPS:	Lipopolysaccharide
NPs:	Nanoparticles
NSCLC:	Non small cell lung cancer
PEG:	Polyethylene glycol
PEI:	Polyethyleneimine
PLGA:	Poly lactic co glycolic acid
PS:	Pulmonary surfactant
PTX:	Paclitaxel
siRNA:	Small interfering RNA

Introduction

The respiratory tract is frequently exposed to the external environment. External environment contain lots of bacteria, fungi and viruses. Such type of pathogenic microorganism causes damage to the upper respiratory tract so, they should be cleared off from lungs. As compare to the upper, lower respiratory tract infection cause serious problems which leads to the death worldwide [1-2]. The respiratory disease is a serious threat to the human as it considered as social as well as economic burden. The diseases related to the respiratory tract include chronic and acute respiratory tract infection, asthma, lung cancer, tuberculosis and cystic fibrosis [3]. Although In current scenario improved and effective diagnostic and improved therapeutic technique is not available for the treatment of such disease [4-5]. In addition, it is challenging for various drugs to reach the lower respiratory tract with effective dose and minimum adverse effects. Therefore, there is a need for effective and novel treatment with efficient dose to treat such types of diseases. Infections of the lower respiratory tract are difficult to treat because the microbes lie deep in the respiratory tract, usually incorporated into a combination of bio film and thick mucus. The treatment of these infections by antibiotics administered orally and/or intravenously requires high doses to maintain therapeutic levels, because only a small fraction of the medications given can reach the mucous side of the lungs through the general circulation. On the other hand, inhaling antimicrobials is the primary source of infection, at the same time, systemic exposure and related side effects are minimized [6-7].

The delivery system for Nano medicines is the application of nanotechnologies in the pharmaceutical field, and showed development perspectives in targeted diagnosis and treatment, delaying the release of medicines, improving the solubility and availability of medicines. The large airway contact area is composed of alveolar cells and cup cells, while the primary bronchiole cells are made up of bronchial epithelial cells and Clara cells. The high permeability and thin barrier of this membrane make the lungs an ideal location for systemic and local drug distribution [8].

In addition, pulmonic administration improves the bioavailability and distribution of drugs to lung sites as well as biocompatibility. The development of nanotechnologies brings a broad new perspective to improve the effects of treating and diagnosing respiratory diseases. However, consideration should also be given

to the possible negative effects of nanoparticles as drug vectors. The toxicity of inhaled nanoparticles has been known to occur for a long time For example, some Nanoparticles, almost like fine dusts and fibres in nature, may induce respiratory and cardiovascular diseases as environmental pollutants [9-11].

Nanoparticles (Nps) in Respiratory System

Characteristics of Nanoparticles for efficient respiratory illness treatment design. Nanoparticles are often inhaled, diffused into the tract and deposited within the alveoli, where they will approach and interact with the epithelial cells and pulmonary surfactant. The characteristics of Nanoparticles, including size, shape, surface charge and wettability, serve a critical role in understanding the interaction between Nanoparticles and organisms. Appropriate properties can't only facilitate their direct delivery to targeted tissues and cells, but also limit their adverse side effects by decreasing drug concentrations in other tissues of the body [12-14].

Surface Charges

The surface charge of NPs determines the interaction between NPs and anionic cell membranes. For instance, Mousseau and Berret observed a stronger interaction between charged NPs and PS compared with charged NPs in vitro, which resulted within the aggregation of NPs and reduced their transfer efficiency. However, in some specific fields, charged NPs have shown obvious advantages. Since charged NPs have the potential to induce damage to cell membranes and organelles, Nano carriers with stronger positive charges might not be a perfect choice for drug delivery systems. A previous study in mice revealed that cationic NPs were mostly related to DCs, whereas anionic particles were mainly internalized by alveolar macrophages. It's possible that the various cellular uptake mechanisms of cationic and anionic NPs might cause different immune effects following pulmonary administration [15-17].

Shape

Shape is another important property that affects the interaction of NPs and cells, and therefore the fate of NPs within the physical body. Previous studies reported that spherical particles were more conducive to cellular internalization than shaped particles. However, Gratton et al reported that rod shaped, cationic, cross linked NPs modified with poly glycol (PEG) were internalized at a better rate than particles of other shapes (spheres, cylinders and cubes). In contrast, it had been reported that gold Nano spheres had better blood circulation and better overall tumour accumulation rate than other shapes (nanodiscs, nanorods and nanocages). Moreover, shape can also be involved in regulating the trans port of NPs on the PS monolayer. A previous study revealed that NPs smaller than the thickness of the PS layer attended be submerged and hardly transported through the PS layer, whereas NPs larger than the thickness of the lung surfactant layer attended be encapsulated by the PS layer. The results of coarse grained molecular dynamics simulations suggested that rod like NPs exhibited stronger penetration and fewer adverse effects on the dipalmitoylphosphatidylcholine (DPPC) monolayer compared with other shapes [18-24].

Size

Among the various characteristics of NPs, particle size may be an exceptional characteristic. Inhaled NPs square measure deposited on the respiratory organ airway in the main via diffusional displacement by the thermal motion between air molecules and also the NPs. The cavity and tracheobronchial deposition of NPs are reportable to be negatively correlate with their size. A previous animal study in pigs performed by Murgia et al discovered that solely very tiny tiny ylated NPs (<100 nm) were able to penetrate into secretion. Compared with giant NPs (>100 nm), NPs with smaller size (<30 nm) were additional appropriate at penetrating biological barriers, together with the air blood barriers. After intranasal immunisation of styrene particles (20 1,000 nm), Blank et al compared the size dependent cellular absorption of those particles on antigen presenting cells at metastasis sites in BALB/c mice. Within the trachea and respiratory organ parenchyma, most of the smaller particles (20 and fifty nm) were absorbed by nerve fibre cells (DCs) compared with larger ones (1,000 nm), conjointly the} smaller ones were also discovered in lung associated body fluid nodes. However, the uptake of cells by alveolar macrophages didn't rely on the scale of particles and bigger particles may simply be phagocytized by respiratory organ macrophages [25-27].

Wettability

The variations in wettability of NPs are typically related to completely different treatment outcomes. Hydrophobic NPs are deemed to act a lot of closely with the charged cell wall in comparison with deliquescent NPs. However, the property of NPs will mimic a danger signal to stimulate the system. Nanogels comprised of deliquescent polymers [poly (sulfobetaine), PEG or poly (carboxybetaine)] were found to be effective in inhibiting immune responses once pneumonic administration, via a discount within the degree of infiltration of inflammatory cells within the BALF and therefore the expression of cytokines (TNF α and IL 6) in a very lipopolysaccharide (LPS) induced inflammatory mouse model. Guzmán et al according that NPs incorporated into chemist monolayers of DPPC may alter the surface organization of the molecules. In comparison neurotic carbon, deliquescent silicon dioxide had stronger influence on DPPC part behaviour [28-30].

Advance in Nanoparticluate Pulmonary Delivery

Benefitting from the progress within the field of materials and technology, a range of innovative nanoparticle systems with manageable properties are developed for drug delivery functions. During this section, we tend to summarize the most recent insights into tailored style of nanoparticles with optimum options to beat the cellular and cellular barriers in infected lungs to accomplish site-specific drug delivery. The interactions of nanoparticles with the various biological barriers powerfully depend upon the chemistry characteristics of the nanoparticles, like their size, shape, surface charge, and surface hydrophobicity. As an example, nanoparticle with sizes but a hundred nm showed superior ability to beat the steric barrier of mucous secretion and EPS, granting adequate mucous secretion and biofilm penetration. Each static and hydrophobic interactions between nanoparticles and also the parts of one-celled barriers offer adhesion that impedes the nanoparticles' diffusion through the mucous secretion and also the EPS. The carboxyl and sulphate teams of the oligosaccharide chains offer glycoprotein with a web electric charge and also the non-glycosylated regions of the glycoprotein in the main contribute to the property [31-40].

Liposomes

The application of liposomes as a drug delivery system has profound effects on pharmacology. Liposomes are a class of lipid vesicles composed mainly of phospholipids and cholesterol. This colloid consists of a self-assembled lipid bilayer with an amphoteric domain and contains an inner water core of the lipid bilayer and an outer envelope. Based on the physical properties of the drug, liposomes can encapsulate drugs of different solubility at the water core or phospholipid bilayer interface, increasing the solubility of the loaded drug by co-solubility The lipid bilayer of liposomes has a composition similar to that of cell membranes in

vivo and not only reduces toxicity, but also increases absorption by allowing liposomes to cross multiple biological barriers. Finally, it improves the therapeutic effect of the drug loading. Alternatively, liposomes can be used as vectors for other functional groups, such as targeted ligands, to provide novel properties for the delivery of therapeutic drugs [41-43]. Additionally, a previous study by Garbuzenko et al tested a variety of Nanomaterial's to select the best carrier for antineoplastic agents, making it a lipid-based non-support versus a non-lipid carrier. In recent decades, liposome delivery system-based Nano medicines have attracted the attention of scientists and clinicians in various areas of respiratory disease. For example, in non-small cell lung cancer (NSCLC) A5 9, a direct mouse model of human lung cancer, Garbuzenko et al received intravenous and intratracheal administration of DOX surrounded by liposomes, antisense, and small oligonucleotides. We compared the effects of. RNA (siRNA) in lung cancer results in much higher concentrations and longer retention times of the three drugs in the lung when administered intratracheally compared to systemic administration by intravenous administration, and topical intratracheal use compared to systemic administration. Showed that it is excellent. Same medicine. .. Similarly, Koshkina et al showed that pulmonary administration of paclitaxel (PTX) with an aerosol liposomal formulation was more effective than intravenous administration in rats. In a mouse model of carbamate-induced lung tumors, Fritz et al showed that liposome-coated clodronic acid reduced macrophage numbers from 50 to to 6 weeks of treatment and reduced significant growth of tumor cells. In addition, a phase I clinical trial by Wittgen et al examined the application of a liposomal formulation of cisplatin in lung cancer. Their results show that this drug delivery system can increase drug accumulation and reduce systemic side effects [44-47].

Solid lipid Nano Particles (SLN)

SLN is another lipid-based material whose structure is slightly different from that of liposomes. SLN has the potential to replace traditional delivery systems due to its many advantages, including targeted drug delivery, controlled release, high drug stability, and high drug availability. Hydrophilic and lipophilic drug packaging, low toxicity of auxiliaries, lack of organic solvents in production such as high pressure homogenization) and large-scale industrial production. Nassimi et al evaluated the toxicity of SLN as a potential nanotransporter in in vitro and ex vivo lung models, and the results show that particle SLN20 (20% phospholipids in lipid matrix) is safe [48,49].

In recent years, GS has been promoting the development of treatments for respiratory diseases as a colloidal drug delivery system. For example, Videira et al studied the anticancer effects of PTX-filled GLS on lung cancer, where lung Nano pharmaceuticals effectively reduce cytotoxicity and cancer progression develops lung metastases in vitro and in vivo. Found to prevent. Furthermore, Castellani et al manipulated SLN-encapsulated grape seed-derived proanthocyanidins for the treatment of chronic respiratory diseases and, through cellular experiments and mouse models, the complex was found in airway epithelial cells, confirmed that oxidative stress and inflammation can be suppressed [50,51].

Furthermore, SLN can be modified to improve targeting, thereby increasing drug accumulation at the target site and reducing systemic toxicity. For the treatment of tuberculosis, Maretti et al used SLN modified with a mannose derivative as a rifampicin Nano carrier to test the potential of a new antituberculosis drug in macrophage cells. Mouse J77. Their results suggest that surfactant-modified SLNs (mannose derivatives) may improve the ability of macrophages to absorb encapsulated drugs. A similar study was conducted by Nimje et al, who found that mannose-bound SLN could deliver rifampicin more efficiently than naked SLN, increase therapeutic efficacy and reduce drug side effects [52-54].

Polymeric Nano Carriers

Polymers are a class of macromolecules that are composed of many small homologous molecules. Polymers are natural (albumin, gelatine, alginate, collagen, cyclodextrin, and chitosan) or synthetic [polylactic acid-co-glycolic acid (PLGA), polyacrylate, polyethyleneimine (PEI), PEG, polyanhydride, and Poly-1-lysine]. Polymers with specific biological and physicochemical advantages are used to create Nano supports for the use of therapeutic and diagnostic agents. Polymer-based Nano supports can deliver a variety of agents, either injected onto the surface of the polymer or dispersed in a polymer matrix [55-57].

Oily Polyester is the most commonly used polymeric Nano support due to its excellent biocompatibility, sustained release, and sufficient biodegradability under physiological conditions. Various forms of polymeric Nano transporters have been used in preclinical experiments for the treatment of respiratory illness. Among them, PLGA has been approved by the FDA for use as a drug delivery system. Ciprofloxacin-loaded NP PLGA and tested its therapeutic effect on cystic fibrosis induced by bacterial infection of Calu-3 and CFBE 1o cells. The results show that Nano medicine has a high drug load and osmotic capacity, which not only allows the continuous high concentration of the drug to be achieved in place, but also reduces the drug dose to reduce side effects. Through in vitro and in vivo experiments, it was found that a sustained-release inhalation system constructed from DOX and PLGA showed high encapsulation efficiency and excellent spraying ability, effectively suppressed cell proliferation, and pulmonary it was revealed that it is suitable for treatment. Cancer metastasis. In study of guinea pigs, encapsulation of PLGA increased the half-life and mean length of stay of the three anti-tuberculosis drugs, thereby improving bioavailability and reduced frequency of administration. In addition, TAS-103 loaded PLGA NP increased drug toxicity to A5 9 lung cancer cells and increased drug levels in rat lungs. PLGA is also considered a good choice for transgenic applications in the treatment of respiratory diseases.

An in vitro study reported that negatively charged Bioadhesives PLGA NPs could be used as an effective non-viral vector for gene therapy in the treatment of lung cancer. Although the PLGA has certain advantages, it also has certain limitations as a pulmonary delivery system. For example, slow breakdown of PLGA can lead to excessive accumulation of PLGA in the airways. The rate of drug degradation depends on the composition and molecular weight of the nanopolymer support, and the time of release varies from weeks to months. In addition, further hydrolysis of PLGA can produce acidic nuclei in the drug delivery device, lower the pH of the microenvironment, and damage enveloped pH-sensitive proteins such as peptides and proteins. In addition, due to the extremely high hydrophobicity of PLGA, the enveloping effect of low molecular weight hydrophilic drugs cannot be avoided, and the hydrophobic surface can cause rapid absorption of proteins, leads to clearance of PLGA by alveolar phagocytic cells.

Conclusion

Nanotechnology has become an important tool for overcoming the shortcomings of drugs and enabling them to passively or actively target specific cells or tissues. This review summarizes the uses and benefits of NPs as a means of drug delivery in respiratory diseases such as lung cancer, asthma, chronic respiratory diseases, cystic fibrosis, tuberculosis, and urinary tract infections. Respiratory. The

combination of nanotechnology has facilitated the development of drugs for the treatment of respiratory diseases based on the benefits of inhalation. However, while preclinical studies show broad development prospects, the most relevant trials are still in the early stages of testing and their clinical efficacy has yet to be validated. Future research should focus on changes in nontherapeutic performance, molecular mechanisms, and potential toxicity during treatment.

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