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Review

Nanoparticles in the treatment of chronic lung diseases

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Abstract

Nanoparticles, although considered a topic of modern medicine, actually have an interesting history. Currently, advances in nanomedicine hold great promise as drug carrier systems for sustained release and targeted delivery of diverse therapeutic agents. Nanoparticles can be defined as complex drug carrier systems which incorporate and protect a certain drug or particle. Nanoparticles can be administered via different routes, such as intravenous injection, oral administration, or pulmonary inhalation. Even though the use of nano-carriers via pulmonary inhalation is heavily debated, this system represents an attractive alternative to the intravenous or oral routes, due to the unique anatomical and physiological features of the lungs and the minimal interactions between the targeted site and other organs. Some of the widely used nano-carriers for the treatment of chronic pulmonary diseases, via pulmonary route, are as follows: polymeric nanoparticles, liposomal nano-carriers, solid lipid nanoparticles, and submicron emulsions. Nano-carrier systems provide the advantage of sustained-drug release in the lung tissue resulting in reduced dosing frequency and improved patient compliance. Further studies focusing on understanding the mechanisms of action of nanoparticles and improving their chemical structure are required in order to better understand the potential long-term risk of excipient toxicity and nanoscale carriers.

Keywords : nanoparticles, chronic lung diseases, therapy, sustained drug release, patient compliance

Highlights

- ✓ In chronic lung diseases, nano-carrier systems provide the advantage of sustained drug release in lung tissue, resulting in reduced dosing frequency and improved patient compliance.
- ✓ Further studies are required in order to better understand the potential long-term risk of excipient toxicity and nanoscale carriers.

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Introduction

Nanoparticles, although considered a topic of modern medicine, actually have an interesting history, as their use dates back to the 9th century Mesopotamia, where they were used by manufacturers to create a glittering effect on the surface of pots. They were created by mixing copper, silver salts, and oxides, together with vinegar, ochre, and clay, on the surface of previously-glazed pottery. The object was then placed in an oven and heated to about 600°C.

The first scientific characterization—no longer in use—in terms of optical properties of nanometric metals was formulated by Michael Faraday in his classic paper "Experimental relations of gold (and other metals) to light". The paper, both philosophical and scientific, described a series of experiments of ultramicroscopic particles of gold in various liquids, in order to establish whether their optical properties suffer any changes under such conditions. Faraday formulates the following statement: "It is well known that when thin leaves of gold or silver are mounted upon glass and heated to a temperature that is well below a red heat (~500 °C), a remarkable change of properties takes place, whereby the continuity of the metallic film is destroyed. The result is that white light is now freely transmitted, reflection is correspondingly diminished, while the electrical resistivity is enormously increased (1).

In the late 1960s, Prof. Speiser at the Swiss Federal Institute of Technology in Zurich developed the first nanoparticles for drug delivery purposes and for vaccines against tetanus, diphtheria, and other infections (2). Currently, further advances in nanomedicine hold a great promise as drug carrier systems for sustained release and targeted delivery of diverse therapeutic agents (3). Nanoparticles can be defined as complex drug carrier systems, which incorporate and protect a certain drug or particle (4). Nanoparticles can be administered via different routes, such as intravenous injection, oral administration, and pulmonary inhalation. Due to their submicron sizes, intravenously injected nanoparticles can easily escape the altered blood vessels, such as those found in tumors, trauma, or inflammatory sites. In these pathological lesions, as a result of the defective lymphatic drainage of these tissues, nanoparticles are retained for longer periods of time (5). Using nanoparticles as oral drug carriers can protect the active ingredient in the gastrointestinal tract against proteolytic enzymes, prolong the action of the drug in the mucous membrane, and facilitate the drug transport across the intestinal mucosa, making this a comfortable drug administration method (4).

Even though the use of nano-carriers via pulmonary inhalation is heavily debated, this system represents an attractive alternative to the intravenous or oral routes, due to the unique anatomical and physiological features of the lungs and the minimal interactions between the targeted site and other organs (6).

Discussions

The purpose of this research was to summarize the current literature regarding the advantages and disadvantages of the use of nanoparticles in the treatment of respiratory diseases, such as COPD (Chronic Obstructive Pulmonary Disease), asthma, lung cancer, or tuberculosis, the most clinical common chronic lung diseases. An important aspect to discuss is the last decade's progress in the development of nano-carrier systems for the treatment of chronic pulmonary diseases, in terms of chemistry, bio-distribution, and toxicity. Over 2,500 papers have been published in the past 10 years regarding nanoparticles, proving the exhaustive efforts that are focused on developing this new and promising class of drugs.

An electronic search in PubMed database and Web of Science was conducted on publications from February 2009 to February 2019. Only studies published in English were included. In the databases, the search used the following keywords "nanoparticles" and "respiratory disease". The studies were then searched manually from the reference list through the databases.

The inclusion criteria were: articles written in English, full-text articles, studies published in the last 10 years, and all studies performed in vitro, ex vivo, and in vivo. Exclusion criteria were literature reviews and studies about nanoparticles that were correlated with diseases other than chronic respiratory ones. The outcome measure in this research was the roles of nanoparticle therapy in chronic pulmonary diseases.

The major advantages of nanoparticle-mediated drug delivery to the lung are attributed to the unique pharmacokinetic and pharmacodynamic properties of the system and the anatomical and physiological particularities of the respiratory tract. The human respiratory tract has a large surface area (greater than $100m^2$), a thin lung-blood barrier (approx. 0.1 microns), and a high perfusion rate, thus providing quick and efficient access to the circulatory system. Nanoparticles are particulate drug carrier systems which incorporate a certain drug in order to coat, protect, and increase its function. Drugs used for the treatment of pulmonary diseases can be administered via oral, intravenous, or inhalation routes, the last being the most

attractive option in terms of low side effects and high bio-distribution (7).

Drug delivery to the lung requires particles sized between 1 and 5 microns administered by means of nebulization, pressurized metered dose inhalers (MDI), and dry powder inhalers (DPI) (8). Metered dose inhalers are breath-actuated auto-halers that release the medication during inhalation, and there are no-breath-actuated pressurized inhalers in which medication is released by pushing the canister down into the holder, such as budesonide/formoterol or fluticasone propionate or salmeterol xinafoate (9). The active ingredients in MDI inhalers are dissolved or suspended in a propellant, and they are delivered via a compact pressurized aerosol dispenser.

Dry powder inhalers are a group of inhalers that contain medication in very fine dry powder form. They are classified into single dose devices, multiple unit dose devices, and multi-dose devices. These tend to be more popular with patients because they are all breath-actuated. Examples of DPI are formoterol fumarate, mometasone furoate, salmeterol xinafoate, tiotropium bromide, and so on (10). The rate required to deliver the medication in MDI inhalers is about 30L/min, while the rate required for DPIs is higher (ranging between 30-120L/min) (10).

In the case of DPI, the force of inhalation plays a key role in the deposition of particles. If the force is insufficient, the particles will not reach the lungs and will be deposited in the upper airways (mouth, pharynx, larynx and trachea). For MDI, despite the high speed of the generated aerosol, the key role is represented by good synchronization between the inhalation and the administration of the drug (9).

For a better penetration through the respiratory mucosa and an enhanced local effect, the idea of administering classic therapies, such as bronchodilators, anti-inflammatories, chemotherapy, or tuberculostatic agents through nano-particulate formulations has emerged.

The pharmacodynamics of nanoparticle carrier systems is as follows: once the nano-carrier formulation reaches the lung, it goes through mucociliary clearance (MCC) and clearance. The mucociliary clearance transports the particles and the mucus produced by the lung epithelium towards the upper airways to be swallowed. Meanwhile, some of the particulate material is recognized by the antigen presenting cells, such as alveolar macrophages and dendritic cells. The alveolar macrophages depredate and possibly deposit the drug, therefore the material ending up here is mostly lost (11). Dendritic cells present the drug to the nearby lymph nodes where they are recognized by the lymphocytes, leading to an immune reaction, thus providing a new alternative for the administration of antigens and vaccines. Only a small part of the inhaled nano-particulate formulations is able to avoid the mucociliary clearance, therefore various muco-penetrative molecules are being researched. Two major ideas have emerged: some studies show that small particles with a hydrophilic surface layer and a slight negative charge have a higher chance of penetrating the mucus (12). Other studies show that the addition of polyethene-glycolic acid to the surface of the nanoparticle (known as the process of PEGylation) provides an increased diffusion in human mucus and prevents the formation of drug aggregates (13).

The major benefits of nanoparticles administered to the lung are as follows: uniform distribution of the drug (14, 15), enhanced solubility and dissolution rate (16, 17), sustained release (18), delivery of various macromolecules (19, 20), and internalization by cells (21, 22).

Some of the widely used nano-carriers for the treatment of chronic pulmonary diseases, via the pulmonary route, are as follows: polymeric nanoparticles, liposomal nano-carriers, solid lipid nanoparticles, and submicron emulsions (23).

- **Polymeric nanoparticles** are composed of biodegradable or biocompatible materials such as polylactic acid, alginic acid, gelatin, and chitosan, which results in prolonged drug release (24). They are currently used in several chronic pulmonary diseases such as asthma, tuberculosis (TB) (25, 26), and pulmonary hypertension (27).
- **Liposomal nano-carriers** are uni-multi-lamellar spherical nanoparticles made of lipid bilayer membranes, including cholesterol and phosphatidylcholine, delivered in a liquid and dry powder form (28-31). The most valuable function of this nano-system is the increase in cellular uptake of the drug due to the presence of cells penetrating peptides. They have proven themselves useful in treating respiratory distress syndrome (32).
- **Solid lipid nano-carriers** are composed of solid lipids, surfactants, and water. They have less or almost no cytotoxic effect compared to the polymer-based carriers, as shown in different studies: in vitro, ex vivo, and in vivo (33-35). Their main use is represented by lung cancer treatment and TB (tuberculosis) vaccine delivery. Solid lipid nano-carriers represent a multifunctional strategy in which a single molecule allows detection, diagnosis, imaging, cell destruction, and delivery of drugs, decreasing drug-related side effects (36, 37). More tolerable to the lungs and major advantages of solid lipid nanoparticles are

the controlled release of drugs with rapid in vivo degradation (38-40).

- **Submicron emulsions** are promising carriers for DNA vaccines (e.g. Mycobacterium tuberculosis) to the lung compared to the commercially available liposomes. The emulsion systems are able to transfect pulmonary epithelial cells, which directly activate dendritic cells, resulting in the stimulation of antigen-specific T-cells (41).

The type of formulation, composition, shape, and size are all important determinants in the pulmonary delivery of nanoparticles (42, 43).

The delivery of the drug requires drug formulations capable of inhalation and delivery of the active component to the lower respiratory tract (44). In vivo, the particle size-dependent regional deposition in the lung is variable, explaining why all particles or droplets must range between 1 μm and 5 μm in diameter (45, 46). In general, particles larger than 5–6 μm are exhaled, while ultrafine particles (1–2 μm) are usually deposited in the bronchioles. Nanoscale particles (<1 μm) can be delivered to the alveoli. Particles smaller than 20 nm, such as dendrimers are also delivered to the alveoli, but they rapidly enter the bloodstream and so become retained in the lungs (47).

In vitro, the endocytosis of nanoparticles is also strongly dependent on their charge (48). As already explained, PEGylation is a well-known process which consists in attaching strands of polyethylene glycol to the surface of certain molecules, thus changing the conformation, electrostatic binding, hydrophobicity, and immunogenicity of the molecule, resulting in enhanced epithelial penetration, slower uptake, aggregation in and degradation of nano-particulate formulations by the reticuloendothelial system, longer steady-state concentrations, less frequent administrations, and lower dosages. The first PEGylated drug approved by FDA in 1990 was ADAGEN, used to treat a form of severe combined immunogenicity syndrome. PEGylation has become a common characteristic of various medications ever since (49).

PEGylation of nano-carriers could be beneficial, by helping to overcome physiological barriers in the alveolar epithelium, thus resulting in enhanced penetration across the mucosal barrier and promoting entry into alveolar epithelial cells (50). Another major impediment has been overcome through the use of PEGylation, that is, the quick uptake, aggregation in, and degradation of nano-particulate formulations by the reticuloendothelial system. Through PEGylating nano-carriers, the frequency of administration and also the dosage can be reduced. Some studies have proven a lower tendency to the aggregation of the PEGylated nano-molecules, versus the non-PEGylated ones. Aggregation can lead to the nanoparticle entrapment in the liver, lungs, or elsewhere due to capillary occlusion (51). So, various types of nanoparticles have been developed over the last decades. These particles are able to enhance the pharmacokinetics of multiple drugs, potentially providing accurate and controlled drug delivery (52).

The phrase “respiratory diseases” comprises multiple disorders affecting the pulmonary system, the more frequent ones being COPD, asthma, lung cancer, and tuberculosis (53). The respiratory tract has several unique advantageous anatomical and physiological features. The large surface area, combined with an extremely thin lung-blood barrier, provides direct access to the central circulation while creating conditions that are well suited for the efficient mass transfer, as shown by in vitro, ex vivo and in vivo studies (54, 55).

Asthma is characterized by the chronic inflammatory disorder of the airways associated with airway hyper-responsiveness, which leads to airway inflammation and in time, to airway remodeling, with negative consequences on the quality of life. The current treatment strategies include inhaled corticosteroids, beta-agonist agents, and anti-leukotrienes. These treatments reduce the symptoms, but do not prevent airway remodeling; moreover, long-term use of corticosteroids may result in immunosuppression and a predisposition to opportunistic infections. Various particles have been evaluated for the treatment of asthma that is refractory to classical therapies: liposomes, solid-lipid NP, telodendrimers, polyethyleneimine, chitosan, dendrimers, polylactic-co-glycolic acid, and CK30PEG (polyethene glycol linked to a 30-mer of poly-L-lysine via a single cysteine residue). CK30PEG is the latest new molecule studied for nanoparticle’s gene delivery therapeutic systems—not yet in use as it is still in phase I clinical trials.

A recently completed clinical trial of inhaled gene therapy has raised many questions about this type of therapy (56). Validated studies indicate that steroids compacted with nanoparticles are able to achieve prolonged and higher benefits at the site of airway inflammation, compared to free inhaled steroids. This is probably a result of the prolonged and higher concentration of drug in the targeted area, resulting in a sustained bronchodilator effect (57). More recently, nano-particulate formulations of interleukin antibodies have proven useful in reducing asthma exacerbations in patients with allergic asthma. Mepolizumab is an interleukin 5 antibody first approved by the FDA in 2015 and showing promising

results in reducing bronchial inflammation (58). Research studies are now trying to incorporate this molecule into nano-particulate formulations in order to enhance its efficiency.

Chronic Obstructive Pulmonary Disease (COPD) comprises emphysema and chronic bronchitis, which result in a vast clinical presentation. Symptoms include difficulty breathing, cough, sputum production, and wheezing. Traditional treatments include anticholinergics, beta agonists, and inhaled corticosteroids, which can control the symptoms but do not cure the underlying disease. Many designs have been reported so far in the attempt to find a nano-therapeutic system that would be able to overcome the challenges of drug delivery in COPD. The most recent and promising model consists of an inhalable dry powder containing dimethyl fumarate, designed by using advanced particle engineering. The majority of the drug particles can reach the lower airways through this new system, thus providing an anti-inflammatory response in these otherwise hard to reach areas, resulting in fewer exacerbations, reduced symptoms such as dyspnea and coughing. This treatment shows great promise, especially in increasing the quality of life in COPD patients (52).

Lung cancer is one of the most common cancers in the world, being the leading cause of cancer death worldwide. Standard therapies currently include chemotherapy and/or surgery. While chemotherapeutic agents effectively kill cancer cells, their use and hence effectiveness are limited by toxicity. The aim of the current research is to create a multifunctional strategy delivered by a single molecule which allows the detection, diagnosis, imaging, cell destruction, and delivery of the drugs, decreasing drug-related side effects. Polymeric micelle systems encoded with a lung-cancer targeting peptide and encapsulated with super magnetic iron oxide and Doxorubicin show great promise in the field of target-specific treatment of lung cancer. Nano-particulate formulations of classic chemotherapeutic agents have proven useful in reducing the chemotherapeutic side effects and increasing the 5-year survival rate (53).

Tuberculosis is the leading cause of preventable deaths worldwide. Nanoparticle-based drug delivery systems may be considered for the treatment of tuberculosis due to the slow and sustained release of drugs such as classic tuberculostatic agents from the solid lipid nanoparticles both in vitro and in vivo, thus meaning the patients will undergo treatment fewer times per week, therefore increasing adherence to treatment and also the quality of life (50, 59, 60).

One of the most debated topics regarding nano-particulate formulations in the treatment of chronic pulmonary diseases are the potential side effects of this therapy. It is well-known that accidentally inhaled nanoparticles such as Diesel smoke or air pollutants are involved in the development of cardiovascular and respiratory diseases, like pulmonary fibrosis and other interstitial diseases. However, therapeutic nanoparticles show different clearance patterns than the toxic ones. It has been shown that non-biodegradable polymers provoke more toxicity and inflammation than biodegradable nanoparticles (54). A recent study reported that hydrophobic materials were the only ones that induced an inflammatory reaction, leading to asthma-like symptoms, while hydrophilic materials did not induce acute respiratory toxicity, which is why they are preferred as often as possible (55).

Conclusions

This review summarizes the potential beneficial effects of nanoparticle therapy in chronic lung diseases. Nano-carrier systems provide the advantage of sustained drug release in lung tissue, resulting in reduced dosing frequency and improved patient compliance. Further studies focusing on understanding the mechanisms of action of nanoparticles and improving their chemical structure are required in order to better understand the potential long-term risk of excipient toxicity and nanoscale carriers.

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All authors have contributed equally to this paper.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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