Short review:

Recent Advances in Nanomedicine for Respiratory Diseases: A Systematic Review

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The present review addresses recent advances and emerging trends in the use of nanotechnology for therapeutic management of respiratory diseases. Nanoparticles, with their unique si e-dependent properties that differ significantly from those observed in bulk materials, have generated considerable research interest worldwide. Nanoparticle based research is ongoing in various areas of clinical medicine and is being increasingly referred to as nanomedicine. There are many nanoparticles currently being developed for respiratory applications. The overall objective of nanoparticle based drug delivery system in respiratory diseases is to selectively target the lung using nanocarrier systems. It is believed that the nano-si ed drug formulations are more effective than the existing micro-si ed aerosols for inhalation, which are conventionally used for therapeutic management of respiratory diseases. The non-invasive mode of drug delivery, ability of the drug to reach the target site and self administration are some of the salient benefits associated with nano-drug based inhalation systems. The toxicity of pulmonary nanomedicine is also addressed and the need for studies to evaluate the safety of nanocarriers for lung delivery emphasi ed.

(The Pulmo - Face; 14:2, 58-61)

INTRODUCTION

Nanotechnology creates novel materials in the nanometer range which has many prospective applications in clinical medicine and research. This rising field has been driven by the information that when a substance is engineered to be nano-sized (less than 100 nm in one dimension), its properties can differ greatly from its bulk-sized counterpart. Nanotechnology helps in building complex structures that can be targeted to specific tissues, have mechanisms for controlled release, and evade rapid clearance.

The term nanomedicine is generally used when nanotechnology is applied to resolve health-care issues. Artificial nanostructures, such as nanoparticles and nanodevices, being of the same size as biological entities, can readily interact with biomolecules on both the cell surface and within the cell. Nanomedical developments range from quantum dots for molecular diagnostic and imaging [(1)] to therapy using nanocarrier and integrated medical nanosystems [(2)], which may perform complex repair actions at the cellular level inside the body in future [(3)].

The purview of this article is to cover recent advances in nanotechnology for therapeutic management of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. The information provided herein is mainly taken from the PubMed articles published over the last few years. The keywords specifically used to generate the literature search for this review paper were: “nanomedicine;” “respiratory diseases;” “COPD;” “asthma;” and “nanotechnology.”

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UNIQUE PROPERTIES OF NANOMEDICINE

Increased relative surface area, and quantum effects are the factors of nanomaterials that can change or enhance properties such as reactivity, strength and electrical characteristics of bulk materials. They can also affect the optical, electrical and magnetic behavior of materials, particularly as the structure or particle size approaches the smaller end of the nanoscale. Material at the nanometer scale exploits its novel physical, chemical and biological properties and offers the possibility of developing new and efficient therapeutic and diagnostic tools.

Nanomedicine has advantages that allow a more targeted drug delivery and a more controllable release of a therapeutic compound. The aim of targeted site dependant drug delivery and controlled release is to better manage drug pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity of systems in the search for improved efficacy. Two aspects drive the progress of nanostructured drug development: route of administration and drug formulation. Due to the large surface area for drug absorption, the lung is a target of choice for nanocarrier systems. The ability to deliver drugs via the lung is particularly attractive as it is non-invasive, can be self administered and avoids first pass metabolism. Inhalable drugs have been available for many years; however, reformulating drugs to be nano-sized, rather than the micron-sized particles that are currently used, offers a number of potential benefits. Nanoparticles are able to penetrate deeper in to the

respiratory tree be, evade clearance by macrophages and enter the respiratory epithelium more easily than larger-sized particles [4]. New drug formulation that takes advantage from material science and nanotechnology give rise for new micro and nanoparticles, liposomes, micelles, dendrimers, liquid crystals, hydrogels, molecularly imprinted polymers, conjugations of biological molecules and synthetic polymers, and in situ forming implants. Such new drug carriers, drug conjugates and drug-nanosystems can be engineered to control degradation, react to stimuli and be site-specific. A successful drug carrier system needs to demonstrate optimal drug loading and release properties, long shelf-life and low toxicity [5].

RESPIRATORY DISEASES AND NANO-MEDICINE

Chronic respiratory diseases like COPD and bronchial asthma represent one of the major global causes of disability and death [5]. The major challenges in drug delivery and therapeutic efficacy of nano-carrier systems in chronic obstructive airway conditions are severe inflammation, airway defense and mucous hyper-secretion [3, 5]. The structural and pathophysiologic findings in both the diseases maybe easily differentiated in the extremes of clinical presentation. However, a significant overlap may exist in individual patients regarding features such as airway wall-thickening or reversibility and airway hyper-responsiveness in lung function tests.

In asthma, inflammation appears to be mediated by allergen-specific CD4+ Th2 cells, leading to eosinophilia and increased count of mast cells. In COPD, the inflammatory response is macrophage and/or neutrophil driven that can be induced by infection and/or by components in cigarette smoke [3-7]. In stable COPD, airway inflammation is characterized by an increased number of T-lymphocytes, particularly CD8+ T cells, macrophages and neutrophils [6 - 9]. Since the major pathway of administering anti-asthma and anti-COPD drug is the aerosolic route, major advantages may be drawn out of nanocarrier systems. Considering the role of selectin in pulmonary infections leading to bronchial asthma and creation of airway hyper-reactivity, the role of a protein nanoparticle P-selectin antagonist with anti-inflammatory effects in allergic airways disease in in-vitro asthmatic models has been evaluated [10]. Using the same concept, Kumar et al were able to obtain encouraging results by using chitosan IFN-genome-pDNA nanoparticles therapy for diagnosis and treatment of allergic asthma in animal model [11]. Kong et al. have also used the same model for asthma and found a similar trend [12].

A suitable model demonstrating the role of nanomedicine in COPD is lacking. There are few reports where liposomal powders (lipospheres and proliposomes) have been used as drugs for dry powder inhalation aerosol delivery. These drugs are similar to internal lung surfactant and offer unique opportunities in pulmonary nanomedicine owing to their enhanced stability and controlled release properties. Pulmonary diseases such as asthma and COPD could greatly benefit from this type of nanomedicine approach where drugs can be delivered in a targeted manner using dry powder inhalers (DPIs) [13]. According to the FDA guidance for (DPI) drug products, α-lactose monohydrate is the only approved sugar that can be used as a large carrier particle in dry powder inhalation aerosol products to fluidize and disperse the respiratory drug while itself not being delivered to the lung. Other novel materials, including phospholipids, specifically lecithin and amino acids (lysine, polylysine) have also been explored for use in pulmonary formulations as excipients that are delivered to the lung [14].

Cystic fibrosis is usually manifested as an autosomal recessive disease and is caused by the dysfunction of the epithelial chloride channel cells due to the mutation in cystic fibrosis trans-membrane regulator gene (CFTR). Nanotechnology has been effectively used to manipulate the CFTR gene by employing DNA nanospheres. A transfection study has demonstrated that plasmid-containing nanospheres implanted in the tracheal lining result in the expression of CFTR in 50% of the cells. Another theory is that the nanospheres change the composition of mucin, which in turn reduces CFTR gene expression [15].

Due to their biocompatibility, surface modification ability, and sustained-release properties, polymeric nanoparticles have been extensively explored using various highly used pulmonary drugs [16, 17]. These pulmonary drugs include anti-asthmatic drugs, anti-tuberculosis drugs, pulmonary hypertension drugs, and anti-cancer drugs [18 - 23]. However, to avoid accumulation of polymer carriers following repeated dosing, the biodegradability and toxicity of the polymers for long term use should be closely examined in the formulation of polymeric nanoparticles for pulmonary delivery.

TOXICITY OF PULMONARY NANOMEDICINE

While considerable attention has been paid towards the development of newly engineered nanomaterials, comparatively less research has been performed to assess the potential hazard of these new materials. Nanomedicine toxicity studies till now have been conducted mostly on materials which are more relevant for environmental and occupational exposures, such as carbon nano tubes (CNTs) and metal oxides. After delivery into the lung, some nanoparticles may be translocated to extrapulmonary sites and reach other target organs by cellular endocytosis, transcytosis, neuronal, epithelial and circulatory translocation and distribution, making them desirable for therapeutic or diagnostic application. However, these features can cause local invasion of leukocytes, increased numbers of inflammatory cells in broncho-alveolar lavage fluid (BALF), and increased cytokine production, all leading to potential toxicity.

Respiratory effects of nanoparticles mainly include inflammation, oxidative stress and functional disturbances. The deposition of nanoparticles in the lung can lead to chronic inflammation, epithelial injury, and further to pulmonary fibrosis. Typical granulomatous reactions have been observed following pulmonary exposures to CNTs [24-26]. A large number of studies have shown that nanoparticle exposure induces functional disturbances, such as airway hyper-reactivity

(AHR) to non-specific stimuli, tissue injury mediated disturbance in respiratory functions [27-32] and aggravation of existing pulmonary inflammation. Formation and accumulation of fibrous connective tissue arising from a complex set of tissue reactions defines pulmonary fibrosis. Traditionally, fibrosis has been viewed as an irreversible process which varies from a restrictive ventilatory defect causing hypoxemia, pulmonary hypertension, and cor pulmonale, to the distortion of lung anatomy inducing bronchiectasis and chronic respiratory infection. There are significant reports of particle-induced pulmonary fibrosis including nanoparticle induced fibrosis. Cases of particle-induced pulmonary fibrosis, namely pneumoconiosis, are mostly occupationally influenced, and are of serious concern around the world. The inhalation of nanoparticles can induce fibrosis, based upon the time of exposure, exposure concentration, and ability to produce free radicals [33].

In context of pulmonary toxicity, it is important to note that computational models predict increased deposition of inhaled nanoparticles in diseased or constricted airways.Nanoparticles have shown increased pulmonary retention in obstructive lung diseases as well [34].

CONCLUSION

Nanocarrier systems can provide the advantage of sustained-release in the lung tissue, resulting in reduced dosing frequency and improved patient compliance. Local delivery of inhalable nanocarriers appear to be a promising alternative to oral or intravenous administration, thus decreasing the incidence of side effects associated with a high drug serum concentration. In pulmonary drug delivery, there is always the potential long-term risk of excipient toxicity and the nanocarrier itself has issues that should be considered during successful product development of pulmonary drug delivery system.

Nevertheless, their inherently small size and surface modification properties opens up a plethora of opportunities for development of innovative controlled drug release systems thereby providing effective pulmonary cell targeting therapeutic platforms.

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