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Nanotechnology and pulmonary delivery to overcome resistance in infectious diseases☆

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ABSTRACT

Used since ancient times especially for the local treatment of pulmonary diseases, lungs and airways are a versatile target route for the administration of both local and systemic drugs. Despite the existence of different platforms and devices for the pulmonary administration of drugs, only a few formulations are marketed, partly due to physiological and technological limitations.
Respiratory infections represent a significant burden to health systems worldwide mainly due to intrahospital infections that more easily affect immune-compromised patients. Moreover, tuberculosis (TB) is an endemic infectious disease in many developing nations and it has resurged in the developed world associated with the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic.
Currently, medicine faces the specter of antibiotic resistance. Besides the development of new anti-infectious drugs, the development of innovative and more efficient delivery systems for drugs that went off patent appears as a promising strategy pursued by the pharmaceutical industry to improve the therapeutic outcomes and to prolong the utilities of their intellectual property portfolio. In this context, nanotechnology-based drug delivery systems (nano-DDS) emerged as a promising approach to circumvent the limitations of conventional formulations and to treat drug resistance, opening the hypothesis for new developments in this area.

Contents

Abbreviations: AmB, amphotericin B deoxycholate; CDs, cyclodextrins; DDS, drug delivery systems; DPI, dry powder inhalers; DSPC, distearoylphosphatidylcholine; EDTA, ethylenediaminetetraacetic acid; GRAS, generally recognized as safe; MAC, *Mycobacterium avium–Mycobacterium intracellulare* complex; MBSA, maleylated bovine serum albumin; MDR-TB, multidrug resistant TB; MIC, minimum inhibitory concentration; mPEG–DSPE, poly(ethylene oxide)-b-distearoyl phosphatidyl-ethanolamin; MRSA, methicillin-resistant *Staphylococcus aureus*; nano-DDS, nanotechnology-based drug delivery systems; NPs, nanoparticles; OPM, *O*-palmitoyl mannan; OPP, *O*-palmitoyl pullulan; *O*-SAP, *O*-steroyl amylopectin; PAM, *p*-aminophenyl-mannopyranoside; PC, phosphatidylcholine; PC:Chol, phosphatidylcholine:cholesterol; PC:Chol:DCP, phosphatidylcholine:cholesterol:dicetylphosphate; PC:Chol:P90, phosphatidylcholine:cholesterol:P90; PLGA, poly(lactide-co-glycolide); pMDI, pressurized metered-dose inhalers; SA-CSO, stearic acid-grafted chitosan oligosaccharide; TB, tuberculosis; XDR-TB, extensively drug-resistant TB.

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1. Introduction

Inhalation of compounds as a means to treat diseases is used since ancient times. The oldest reports came from China and India around 2000 BC and are related to the inhalation of smoke from burned herbal preparations based on *Ephedra sinica* or *Daturastramonium* to treat asthma, respectively [1,2]. Pedanus Discorides (40–90 AD) the Greek physician, surgeon, pharmacologist, botanist and author of *De Materia Medica* (considered the first pharmacopeia) as well as Aelius Galenus (129–199/217 AD) prescribed inhaled sulfur vapors to their patients [3]. Although the word "inhaler" was used for the first time by the English physician John Mudge in 1778 to describe his invention, the first therapeutic inhalation device is attributed to Hippocrates (460–377 BC) [1,2]. Through the years, many compounds and mixtures were proposed and used to treat different diseases using various methods for inhalation. From ceramic inhalers, to combustible powders, burning papers and liquid atomizers. Very curious and popular ways to inhale compounds in the 19th and 20th centuries were the asthma cigarettes which were withdrawn from the market in 1992 [1,3]. The inhalation of vapor from solutions of picric acid, tar, iodine or sulfuric acid was very popular in the 20th century to treat TB and other infections, especially in spas [3]. The first mentions regarding inhalation of antibiotics such as penicillin by nebulization to treat pulmonary infections were published in the 1940s [3–7]. Nowadays, inhaled drugs are preferentially administered *via* dry powder inhalers (DPI) and pressurized metered-dose inhalers (pMDI), being also used as nebulizers in hospitals.

Despite inhalation being started as a route to treat diseases constrained to the respiratory tract, with scientific and technological advances, a change in paradigm took place and over the years, inhalation has been clinically evaluated and used to treat both local and systemic diseases [8] such as asthma [9], TB [10] and other bacterial infections [11], influenza virus infection [12], fungal infections [13], cystic fibrosis [14], chronic obstructive pulmonary disease [15], diabetes [16] or cancer [17,18]. Moreover, inhalation has been also tested as a non-invasive vaccination platform [19,20].

Driven by the progress in the nanomedicine field, many researchers developed innovative formulations with improved biopharmaceutical features [21,22], allowing the pulmonary administration of many drugs that otherwise could not be administered by inhalation. Such formulations represented promising, although preliminary, alternatives to conventional inhaled formulations [23,24]. In this context, a new door has been opened in the field of inhalation therapy and new advances could be expected in the near future.

This work reviews the state-of-the-art regarding the use of nanotechnology in the development of inhalatory formulations for the treatment of pulmonary and systemic infectious diseases with the emphasis on overcoming drug resistance.

2. Lung and respiratory infectious diseases

Lungs and airways are a site for gas exchange and contact with the exterior, being exposed to organic, inorganic and biological components that can cause disease. There are a variety of bacterial, viral, fungal and parasitic infections that affect the lungs and can progress toward systemic infection, including pneumonia, TB, influenza, aspergillosis, among others. Infections of the lower respiratory tract are among the top three major causes of morbidity worldwide and first in low-income countries, being responsible for approximately 3.5 million deaths annually [25].

2.1. Pneumonia

Pneumonia is a common infectious pulmonary disease that has many etiological agents, including bacteria, viruses and fungi such as *Streptococcus pneumonia*, *Haemophilus influenzae* type b, *Acinetobacter baumannii*, *Klebsiella pneumonia*, *Moraxella catarrhalis*, human respiratory syncytial virus, human parainfluenza virus, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila* or *Pneumocystis jiroveci*. It is the leading cause of death in children worldwide killing annually around 1.8 million children under the age of five years [26,27]. Nosocomial pneumonia, especially in ventilated patients, is unfortunately frequent and represents more than 50% of antibiotic prescriptions in intensive care units [28]. Also, the development of resistant strains in hospitals is causing a great deal of concern among health professionals. The therapy is chosen according to the etiological agent and the severity of the disease, the reason why it is imperative to identify the etiological agent and its sensitiveness to the available therapeutic portfolio in order to treat the patient in a rational way and to prevent the development of resistant strains.

2.2. Tuberculosis

TB is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* that primarily but not exclusively affects the lungs. It is the second leading cause of death from an infectious disease worldwide being declared a global public health emergency by the World Health Organization in 1993, a distinction never granted to any other disease. In 2011, there were around 8.7 million incident cases of TB, 1 million deaths among HIV-negative people and an additional 0.43 million deaths from HIV-associated TB [29]. The current therapy includes long-term multiple dose oral administration of various drugs, which sometimes leads to low patient compliance and therefore to the development of multidrug-resistant strains referred to as multidrug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). The first-line drugs used in the treatment of standard TB are rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin [30,31]. At the moment new drugs are in clinical trials [32] constituting a hope for the treatment of resistant forms of the disease. In addition to the development of resistance, the difficulty to treat TB stems from the fact that when administered systemically many anti-TB drugs fail to reach the lungs or penetrate into the alveolar macrophages, the reservoir of *M. tuberculosis* [31,33]. *M. tuberculosis* persists in macrophages within a granuloma formed in the lungs of the infected hosts. Thus, traditional drug chemotherapy has serious limitations particularly the drug internalization and cytosolic availability on the infected phagocytic cells [34]. This phenomenon has driven many researchers to develop drug delivery systems (DDS) that improve the treatment of such burden.

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