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The formulation of nanomedicines for treating tuberculosis☆

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ABSTRACT

Recent estimates indicate that tuberculosis (TB) is the leading cause of death worldwide, alongside the human immunodeficiency virus (HIV) infection. The current treatment is effective, but is associated with severe adverse-effects and noncompliance to prescribed regimens. An alternative route of drug delivery may improve the performance of existing drugs, which may have a key importance in TB control and eradication. Recent advances and emerging technologies in nanoscale systems, particularly nanoparticles (NPs), have the potential to transform such approach to human health and disease. Until now, several nanodelivery systems for the pulmonary administration of anti-TB drugs have been intensively studied and their utility as an alternative to the classical TB treatment has been suggested. In this context, this review provides a comprehensive analysis of recent progress in nanodelivery systems for pulmonary administration of anti-TB drugs. Additionally, more convenient and cost-effective alternatives for the lung delivery, different types of NPs for oral and topical are also being considered, and summarized in this review. Lastly, the future of this growing field and its potential impact will be discussed.

Contents

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1. Introduction

Tuberculosis (TB) is still far from being a health concern of the past. Although less frequent in Europe and North America, it has a strong prevalence in Africa, Asia and South America [1,2]. In 2014, the World Health Organization (WHO) reported 9.6 million new cases of TB, which resulted in 1.5 million deaths, making it the leading cause of death in the world from infectious diseases [2]. TB is caused by the infection of *Mycobacterium tuberculosis* (MTB) [3]. It can affect practically all organs of the human body, but the lung is of particular high incidence, being designed as pulmonary TB [4,5]. This is expected since the infection starts with the inhalation of infectious aerosol particles released from close contacts, leading the bacteria directly to the lung. Due to their size, the bacilli are able to reach the pulmonary alveoli, where they are phagocytized by the alveolar macrophages (AMs) (Fig. 1) [6,7].

Inside the AMs, the bacilli resist to the bactericidal mechanisms of the macrophage by preventing phagosome-lysosome fusion (phagolysosome) [8]. Therefore, they can multiply and eventually escape from the lung through the bloodstream and lymphatic system, spreading to other organs of the body, resulting in extrapulmonary TB [9,10].

It is estimated that one-third of the world's population is latently infected with MTB. Latent individuals do not transmit the disease to others and latent infection can only progress to an active form of disease in 5%–10% of the cases [2]. However, there are some conditions that are associated with high-risk of susceptibility to MTB infection, namely HIV, diabetes, long-term use of corticosteroids, TNF-α blockers, polymorphisms in vitamin D receptors or in *IL-12* and *IFN-γ* genes, malnutrition and smoking [2,11]. Recently, WHO proposed the eradication of TB until 2050 and although possible, constitutes an ambitious goal to approach, requiring more effective technologies [2]. The development of nanodelivery systems will provide an opportunity to exploit the inhalatory route, which has particular interest in the release of anti-TB drugs directly on the primary organ affected by TB (i.e., lungs). Thereby, it is possible to achieve a high local concentration of drugs in AMs, a reduction of systemic adverse-effects of the drugs as well as the frequency of administration, which ultimately leads to the increase of patient compliance and better efficacy of treatment [12–14]. In this context, the present review provides an overview on the recent progress in nanodelivery systems for pulmonary administration of anti-TB drugs, discussing the drawbacks of current treatment; the advantages of pulmonary delivery; different types of NPs for encapsulation and release of anti-TB drugs, and the challenges that must be overcome to obtaining a more effective and compliant therapy. Furthermore, this review will provide an overview of other non-invasive routes that have been explored for TB treatment.

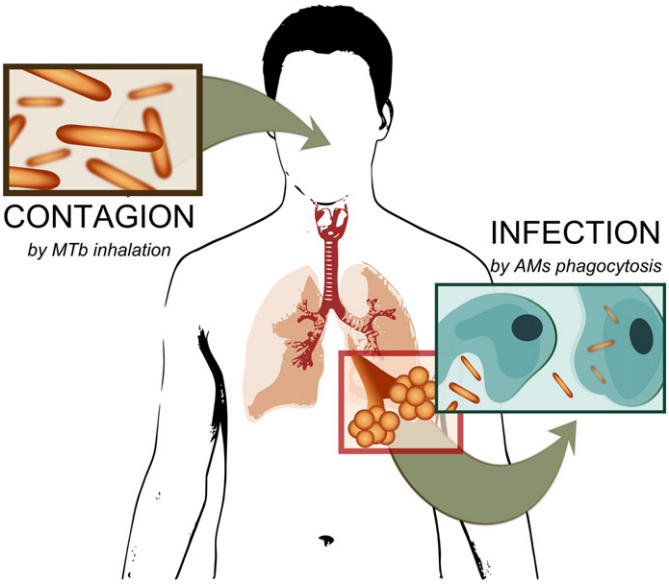

Fig. 1. Schematic representation of the infection by MTB.

2. TB current therapy and limitations

Currently available chemotherapy includes first-line drugs, such as isoniazid (INH), pyrazinamide (PZA), rifampicin (RIF) and ethambutol (EMB); second-line drugs, such as injectable agents (streptomycin, kanamycin, amikacin, capreomycin and viomycin), fluoroquinolones (ofloxacin, levofloxacin, gatifloxacin and moxifloxacin) and other oral agents (ethionamide, prothionamide, cycloserine, terizidone and *para*-amino salicylic acid) [15–17].

According to the WHO guidelines, the standard regimen for TB treatment includes daily administration of INH, RIF, PZA and EMB for 2 months, followed by daily administration of INH and RIF for further 4 months [2].

The second-line drugs are used when treatment with first-line drugs fails or in presence of multidrug-resistant TB cases (MDR-TB). These drugs are less effective, more toxic, and unavailable in many countries due to high costs [2]. Up to December of 2012, the most recent drugs dated back 50 years [18]. Sarkar et al. (2011) emphasized how essential further research in new drug target is needed in order to fight drug resistant TB [19]. There are several new drug candidates currently in research and in clinical trials, and recently two new drugs (bedaquiline and delamanid) have been approved for the treatment of MDR-TB, when other alternatives are not available [2]. Bedaquiline was approved by the Food and Drug Administration (FDA) in December 2012 and has completed phase II trials. However, in order to optimize treatment regimens, phase III trials and phase IV studies are needed [20]. Delamanid was approved by the European Medicine Agency (EMA) in April 2014 and is currently being tested in a phase III clinical trial for the treatment of MDR-TB in adults and in children [20]. Also, several existing drugs are in a state of re-evaluation [18].

The current treatment is usually associated with severe adverse-effects, resulting in poor compliance, which is one of the main reasons for the appearance of multidrug resistant strains and treatment's failure [6,21,22]. Moreover, the current therapies have a limited ability to penetrate granulomas and have reduced effects on dormant bacilli [23]. In this context, improved treatments are needed to shorten TB treatment duration, prevent resistance and reduce lung injury.

Besides the above-mentioned limitations, the administration routes have also critical challenges. The oral route is the most convenient and least expensive; however, prolonged administration of high doses is needed and sub-therapeutic levels of anti-TB drugs reach the site of infection, due to the slower onset of action, the hepatic first-pass metabolism and harsh gastro-intestinal absorption [14,24]. The oral route is also associated with severe side effects as a result of high systemic exposure [13,25]. Compared to the oral route, the parenteral and pulmonary routes have highest bioavailability and are not subject to first-pass metabolism [14]. Nevertheless, parenteral administration is a painful route of administration and requires the presence of healthcare workers [26]. In this context, direct lung delivery of anti-TB drugs using pulmonary delivery systems could be advantageous and will be discussed in more detail in the next section.

3. The pulmonary administration route: Advantages and challenges

Lung is the most important route of access in the case of infection by MTB [27,28], being the inhalatory route for drug delivery an exciting hypothesis to be explored in order to fight TB disease [29–31]. Indeed, the lung is the ideal target site of anti-TB drug delivery and could provide a noninvasive delivery portal, requiring lower administration doses for achieving a better efficacy and toxicity reduction in comparison with oral route [7]. Lung mucosa has a large surface of absorption, a thin alveolar epithelium and an extensive vascularization from which drugs may