Materials Science & Engineering C xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Materials Science & Engineering C

journal homepage: www.elsevier.com/locate/msec

Review

Exploring inhalable polymeric dry powders for anti-tuberculosis drug delivery

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ARTICLE INFO

Keywords:
Polymeric materials
Dry powders
Microparticulate systems
Drug targeting
Alveolar macrophages
Tuberculosis

ABSTRACT

The growing interest on polymeric delivery systems for pulmonary administration of drugs anticipates a more direct and efficient treatment of diseases such as tuberculosis (TB) that uses the pulmonary route as the natural route of infection. Polymeric microparticles or nano-in-microparticles offer target delivery of drugs to the lungs and the potential to control and sustain drug release within TB infected macrophages improving the efficiency of the anti-TB treatment and reducing side effects. In a dry powder form these inhalable delivery systems have increased stability and prolonged storage time without requiring refrigeration, besides being cost-effective and patient convenient.

Thus, this review aims to compile the recent innovations of inhalable polymeric dry powder systems for the delivery of anti-TB drugs exploring the methods of production, aerodynamic characterization and the efficacy of targeted drug delivery systems using *in vitro* and *in vivo* models of the disease. Advanced knowledge and promising outcomes of these systems are anticipated to simplify and revolutionize the pulmonary drug delivery and to contribute towards more effective anti-TB treatments.

1. Introduction

Tuberculosis (TB), caused by infections with *Mycobacterium tuberculosis* (Mtb), is an infectious disease of enormous public health impact. TB is an airborne disease initiated by the inhalation of infected droplets that travel the upper respiratory tract and bronchi, being deposited in the lower airways. Here, Mtb is thought to be recognized and phagocytosed by macrophages, specifically alveolar macrophages. In the majority of cases, this initial interaction between Mtb and immune cells results in the development of a host protective response capable of eliminating the invading pathogen. In some cases however, the immune response does not eliminate the infection thereby resulting

Abbreviations[1]: ALG, alginate; Cm, capreomycin; CHI, chitosan; DPIs, dry powder inhalers; E, ethambutol; EC, ethyl cellulose; ECM, extracellular matrix; Eto, ethionamide; FPF, fine particle fraction; HA, hyaluronic acid; HIP/PCA, hydrophobic ion-pairing/precipitation with a compressed anti-solvent; HPMC, hydroxy propyl methyl cellulose; I, isoniazid; IL-6, interleukin-6; I-PCL, isoniazid loaded poly-caprolactone; LBG, Locust Bean Gum; LS, lysine; MAN, mannitol; MDR-TB, multidrug-resistant tuberculosis; MIC, minimum inhibitory concentration; m-LS-co-ALG, mannosylated lysine conjugated to alginate; MMAD, mass median aerodynamic diameter; MNPs, magnetic nanoparticles; Mtb, *Mycobacterium tuberculosis*; NO, nitric oxide; Ofx, ofloxacin; Ofx-HA, ofloxacin loaded hyaluronic acid; PAS, para-aminosalicylic acid; PBS, phosphate buffered saline; PCL, poly-caprolactone; PLA, polylactide; PLGA, poly(lactide-co-glycolide); PNAPs, porous nanoaggregate particles; Rbt, rifabutin; Rpt, rifapentine; R, rifampicin; R-PLGA, rifampicin loaded PLGA; RR-TB, rifampicin-resistant tuberculosis; SAS, supercritical anti-solvent process; SCO_2, supercritical carbon dioxide; SD, spray-drying; SE, solvent evaporation; SLF, simulated lung fluid; SPG, shirasu porous glass; SPIONs, superparamagnetic iron oxide nanoparticles; TB, tuberculosis; TNF-α, tumor necrosis factor - α; TPP, tripolyphospate; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide

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[1] Drug abbreviation is in accordance to WHO nomenclature.

https://doi.org/10.1016/j.msec.2018.09.004
Received 7 March 2018; Received in revised form 29 August 2018; Accepted 3 September 2018

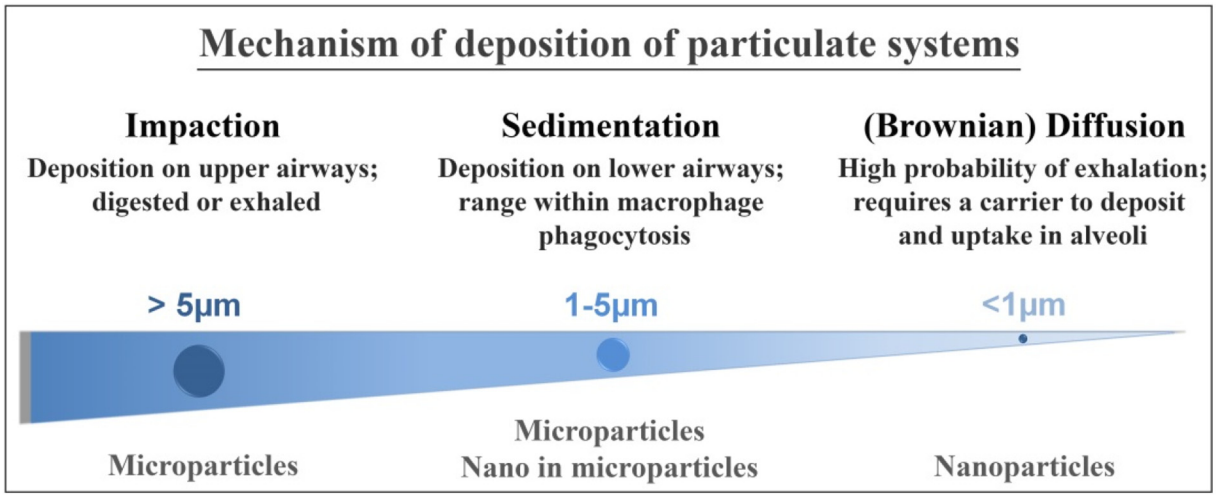

Fig. 1. Schematic representation of the particle deposition within the upper or lower airways considering their dimensions and the type of carrier systems used for their delivery.

in a spectrum of disease with different phenotypes and clinical manifestations [1]. It is estimated that approximately one-third of the world population has contacted with Mtb and part of this population is likely latently infected [2]. Although these individuals do not show signs or symptoms of TB, as the bacteria proliferation is under immune control, they have a 10% increased risk of progressing into active TB during their life time being therefore important reservoirs for transmission [3].

The current anti-TB therapy protocols comprise of a six-month combination course of rifampicin (R), isoniazid (I), pyrazinamide (Z) and ethambutol (E), which are first-line anti-TB drugs. All four drugs are taken during the first two months of the treatment following a period of four months where only rifampicin and isoniazid are taken. Although the success rate of this regimen has been estimated to be over 85% [2], the full length of treatment is crucial for the effective and complete eradication of the pathogen. However, the incorrect use of anti-TB drugs or the use of ineffective drug formulations such as single drug regimen, poor quality medicines or inappropriate storage conditions and premature treatment interruption due to the long duration of the therapeutic regimen and the associated toxic side effects, lead to drug resistance [2].

Treatment for drug resistant strains, which include rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) is longer (up to 2 years) and requires more expensive and more toxic drugs with treatment success rates lower than 54% [2].

Therefore, in addition to classical drug discovery strategies, new approaches are urgently needed to get a faster, more efficient and less harmful treatment. In this regard, the development of novel therapies aiming at pulmonary delivery and drug targeting to the site of infection could be a promising solution to allow a sustainable and controlled release of medicines with therapeutic action, while decreasing the dosage and frequency of conventional chemotherapy and minimizing side effects. Moreover, these approaches may lead to a higher efficiency of the treatment and to a higher patient compliance, minimizing the risk of therapy failure and the development of drug resistant strains.

2. Delivery of anti-tuberculosis drugs to the lungs

2.1. Advantages of the pulmonary route

Despite the natural barriers to prevent invasion of unwanted airborne particles or living entities, such as airway geometry, humidity, mucociliary clearance and resident populations of macrophages, the lungs are constantly challenged with infectious agents, including Mtb, which make these air-filled organs an attractive target for drug delivery strategies as it provides direct access to the infection site. Delivery systems for TB treatment through the pulmonary route present advantages when compared to the conventional oral and injectable routes. These include drug delivery directly to the infected area, increasing local drug concentration which will impact in bacterial burden and reduce the systemic dosage of the drug [4–13]. Additionally, inhalable systems avoid unwanted side effects often caused by drug metabolism in the gastrointestinal tract before the drug reaches the systemic circulation [4–13]. Unlike the injectable route, inhalation is a pain free and self-administrable delivery means favoring patient convenience and compliance to the treatment.

2.2. Particulate carriers as inhalable delivery systems

Pure drug formulations are typically burst released in the lungs and rapidly undergo unspecific distribution [5,14–18]. In order to achieve a more efficient solution, therapeutic agents can be formulated into particulate carrier systems such as microparticles, nanoparticles, liposomes, micelles or dendrimers. Such systems allow protection of drugs from direct contact with the lung tissue, avoiding early degradation, preclude rapid clearance from the body and assist the control and sustain release of drugs over long periods of time. Particulate carriers also reduce drug toxicity, circumvent undesirable physicochemical properties of the drugs (*e.g.* low water solubility) and improve drug uptake by macrophages [19].

In recent years the advantages of inhalable particulate carrier systems have been allied to the benefits of dry powder formulations to be delivered by dry powder inhalers (DPIs) for an improved drug delivery system. Dry powder formulations have improved stability as a result of its dry form, do not require refrigeration and allow longer storage periods. Formulations are often combined with pharmaceutically suitable excipients such as lactose, leucine, mannitol or trehalose to improve processing and aerodynamic properties [20,21]. DPIs are propellant free, portable, easy to use and cost-effective devices. Moreover, DPIs are activated by the inspiration effort of patients, allowing a rapid and higher dose administration and a more efficient pulmonary drug deposition [22,23]. Thus, DPIs are currently considered the most convenient and suitable alternative for inhaling anti-TB drugs [24].

2.3. Design and features of inhalable particulate systems

Medicinal particles are designed and developed so their deposition in the respiratory tract can be predicted rather precisely (Fig. 1). The