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Review

Nanostructured drug delivery for better management of tuberculosis

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ABSTRACT

With almost 30% of the world population suffering from tuberculosis (TB) including its resurgence in the developed world, better management of this global threat is highly desired. The emergence of multidrug-resistant TB (MDR-TB) against first-line drugs and extensively drug resistant TB (XDR-TB) due to misuse of second-line antitubercular drugs (ATDs) is a further concern. Recommended treatment involves long term and multiple drug therapy with severe side effects. In this context, nanostructured systems efficiently encapsulating considerable amounts of ATDs, eliciting controlled, sustained and more profound effect to overcome the need to administer ATDs at high and frequent doses, would assist in improving patient compliance and circumvent hepatotoxicity and/or nephrotoxicity/ocular toxicity/ototoxicity associated with the prevalent first-line chemotherapy. Nanostructured delivery systems constitute a wide range of systems varying from liposomes, micelles, micro- and nanoemulsions, to polymeric nanoparticles (PNPs) and solid lipid nanoparticles (SLNs). Improved bioavailability, solubility, stability and biocompatibility make them an ideal choice for delivery of ATDs. Present review comprehensively covers research carried out on first-line antitubercular drug therapy using these nanostructured systems.

Contents

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1. Introduction

Tuberculosis (TB), a persistent and lethal infectious disease [1], is one of the major challenges in modern day community health [2]. Regardless of potentially remedial pharmacotherapies being available for over 50 years, TB remains the most important cause of avertable deaths. Although TB appears as a chronic disease with comparatively slow development, multidrug-resistant strains can kill immunocompromised patients in very short periods of time [3].

Nanotechnology with its sophistication and advanced techniques has provided us a new tool to understand the scientific developments at a nanoscale [4] and treat dreadful diseases such as tuberculosis and AIDS with a greater ease using nanoparticles as drug delivery systems. Confronted with frequent therapeutic failures and emergence of multidrug resistance strains, researchers have developed novel ways to defy drug resistance, to restrict the treatment duration and more importantly to lessen side effects, toxicity and drug interactions. The present review discusses hurdles in the effective treatment of TB and use of nanostructured delivery systems to counter these problems.

2. Tuberculosis: some key facts

2.1. Epidemiology

After HIV/AIDS, TB is the most commonly occurring and fatal infectious disease [5]. Roughly 2 billion people at present are infected worldwide with *Mycobacterium tuberculosis*, representing about 30% of the total population. In 2012, 8.6 million people fell ill with TB and 1.3 million died from TB. Though prevalent in budding countries where elevated mortality indexes have been reported [6], howsoever, infection has also resurged significantly in the urbanized countries. A WHO self study estimated that every second a new person is infected with TB [7]. Though billions of dollars are spent each year and the governments all over the world stand committed to the eradication of TB, however the disease still remains out of bound, infecting millions and killing thousands of infected population.

2.2. Nature of causative agent

M. tuberculosis, is an acid fast bacteria, which forms acid-stable complexes with arylmethane dyes [8]. The Mycobacteria are plentiful in soil and water, but *M. tuberculosis* is mainly identified as a pathogen which lives in the host and several species of the *M. tuberculosis* complex have specifically adapted their genetic structure to infect human populations.

2.3. Emergence of MDR and XDR

Mismanagement of first-line drugs results in the emergence of multidrug-resistant TB (MDR-TB), cure for which takes even longer. It requires use of second-line drugs, which are costlier and show more extensive and severe undesirable effects. Globally, only 48% of MDR-TB patients in the 2010 cohort of detected cases were successfully treated, and high mortality rates and poor follow-up was reflected. Globally in 2012, an estimate of 450 000 people, spread over virtually all the surveyed countries developed MDR-TB and there were an estimated 170,000 deaths from MDR-TB.

When the second-line ATDs are misused (including use of quinolones for normal non-mycobacterial infections), extensively drug resistant TB (XDR-TB) which is resistant to both first and second line anti-TB drugs [9–11] results. XDR-TB strains have been reported from South Africa and other parts of the world, with its high occurrence in HIV-positive individuals.

2.4. Secondary infections in HIV patients

It is estimated that 1/3 of the 36 million people on earth with HIV/AIDS are co-infected with *M. tuberculosis* [12]. This co-infection has been named the "cursed duet," requiring approximately 30% of the yearly income of an infected household in direct and indirect costs, thus becoming a socio-economic calamity for these families [13].

Countries with the maximum TB/HIV co-infection rates exist in Sub-Saharan Africa. Worldwide, the biggest increase in co-infection with TB and HIV has taken place in the 25–44 year old population [14]. Since this age group generally involves the active workforce of any country, hence the consequent economic impact is huge.

3. Antitubercular drug (ATD) therapy: issues and concerns

3.1. WHO treatment guidelines

WHO recommends the use of first line ATDs (Table 1) in TB patients at the onset of the disease. The most effective pharmacotherapy is composed of a multi-drug regimen of isoniazid (INH), pyrazinamide (PZA) and rifampicin (RIF). The first 2 months involve intensive therapy with these three agents together with ethambutol (EMB) [15,16]. For the remaining 4 months, RIF and INH are administered. These four drugs collectively with streptomycin (parenteral aminoglycoside) represent the so-called first-line treatment.

To simplify dosing schedules and to minimize mono-therapy-associated resistance to RIF, the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) suggests administration of fixed dose combination (FDC) of RIF and INH plus PZA or PZA with EMB [17,18]; FDC's combine at least 2 first-line ATDs drugs in one single formulation.

All the ATDs (except RIF) are hydrophilic in nature (Table 1), and invariably manifest severe side effects especially upon long term use. Any carrier system which can help improve the permeability of these agents (low or negative log P as shown in Table 1, indicates poor permeability of these ATDs; BCS class III) will result in improved effectiveness at lower dose with lesser incidence of side effects. Later will in turn lead to improved compliance with lowered health costs. It is in this context that encapsulation technology (micro- or nano-encapsulation) may play an important role for formulating ATDs into sustained-release systems.

Treatment of MDR-TB comprises the administration of PZA concurrently with second-line drugs such as ethionamide, prothionamide, cycloserine, capreomycin, p-aminosalicylic acid or fluoroquinolones [27]. The second-line drugs exhibit more toxicity, are more expensive and are less potent than the first-line agents.

The present review is majorly focused on the use and development of first-line ATDs.

3.2. Major issues related to therapy

To assure therapeutic effectiveness, extended treatments (9–12 months) are usually recommended [28]. In this regard, low patient compliance and obedience to the dosage regimens turn into critical drawbacks of the pharmacotherapy. Variable bioavailability of these ATDs further creates an additional crucial limitation [29].

Amongst HIV/TB co-infected patients, RIF and EMB show a decline in intestinal absorption [28]. Generally variable bioavailability of RIF is otherwise also a major clinical problem [30]. It also displays a strong pH-dependent solubility (1 part in 5, 10, 250, and 360 parts of water at pH-values of 1.5, 2, 5.3, and 7.5, respectively, at 25 °C) [3,31]. RIF displays low aqueous solubility and moderately good absorption in the stomach and was earlier classified as Class II drug, according to the BCS [32] but has later been reclassified as BCS class IV drug [32]. Absorption of RIF from any FDC which also incorporates INH, is significantly compromised due to its reaction with INH, in the gastric medium, to