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Review Article

SUSTAINED RELEASE APPROACHES TOWARDS THE CHEMOTHERAPY OF TUBERCULOSIS

Sharma Shubham*, Dubey Nidhi

School of Pharmacy, Devi Ahilya Vishwavidyalaya Ring Road, Indore, Madhya Pradesh, India

**Corresponding author: shubham.sam53@gmail.com*

ABSTRACT

Tuberculosis is a most important killer of young adults worldwide and the global blight of multi-drug resistant tuberculosis is reaching epidemic proportions. It is endemic in most developing countries and resurgent in developed and developing countries with high rates of human immune insufficiency virus infection. This article reviews the current situation in terms of drug delivery approaches for tuberculosis chemotherapy. A number of novel implant, microparticulate and a variety of other carrier-based drug delivery systems incorporating the principal anti-tuberculosis agents have been made-up that either target the site of tuberculosis infection or reduce the dosing occurrence with the aim of improving patient outcomes. These developments in drug delivery represent attractive options with noteworthy merit, on the other hand, there is a necessity to manufacture an oral system, which directly addresses issues of unacceptable rifampicin bioavailability in fixed-dose combinations. This is fostered by the need to deliver medications to patients more efficiently and with fewer side effects, especially in developing countries. The fabrication of a polymeric once-daily oral multi particulate fixed-dose combination of the principal anti-tuberculosis drugs, which attains segregated delivery of rifampicin and isoniazid for improved rifampicin bioavailability, could be a step in the right direction in addressing issues of treatment failure due to patient non-compliance.

Keywords: Rifampicin, Tuberculosis, Chemotherapy, Bioavailability.

1. INTRODUCTION

Tuberculosis (TB), caused by the bacterium *Mycobacterium tuberculosis*, remains a most lethal disease in humans. The tubercle bacillus has tremendous ability to cope with the human immune system and has developed the ability to survive and do well within macrophage phagosomes. Despite technological advances, TB continues to threaten humans. According to the World Health Organization's 2011 global report on TB 2011 World Health Organization (WHO) report, [1] 8.8 million TB cases were reported in this year, approximately 1.35 million of which were fatal with an additional 0.35 million fatalities in individuals with HIV. TB remains among the three major causes of death among females aged 15-44 years old and approximately 320,000 women died due to TB in 2010. The identification and suitable treatment of multidrug-resistant TB (MDR-TB) remain the most important aspects to be addressed. Furthermore, TB's resistance to contemporary TB antibiotics is due to its dormant form in the host cells. It is known that rifampin, isoniazid, and ethambutol (but not pyrazinamide) require bacteria to reproduce in order to perform their function. It is thought that the bacteria's ability to remain dormant allows them to be phenotypically resistant to prescribed antibiotics [2, 3]. As is well known, drug development is a very long process requiring significant funding and much effort. At the end of the process, it is often still not clear whether the target drug is safe for humans, thus there has been no new anti-TB drug on the market for almost five decades. Researchers are therefore increasingly drawn to biocompatible drug-delivery systems (DDSs) as they can be fabricated to target the specific site of disease, thus reduce side effects in healthy tissues, and prevent drug degradation in transit to the target site. Furthermore, DDSs can maintain the same or a higher level of therapeutic effect using the same, or even in some cases, a lower quantity of drug. Most importantly, the developed DDSs can be used for newly developed drugs. Many DDSs have been developed for anti-TB drugs. They can be classified either by type of system such as biocompatible organic polymer, inorganic, organic–inorganic hybrid, and dendrimer, or they can be classified according to their size, for example, macro, micro, and nano material. In this review, we review some of the most important systems.

2. TYPES OF TUBERCULOSIS

TB can be categorized into one of three main types: drug-susceptible TB (DS-TB), multidrug-resistant TB (MDR-TB), or extensively drug-resistant TB (XDR-TB).

2.1. DS-TB

DS-TB is the most common form of TB and is susceptible to the four first-line medicines: rifampin, isoniazid, ethambutol, and pyrazinamide.

2.2. MDR-TB

It is very difficult to treat TB that has become resistant to multiple drugs, especially to more powerful drugs such as isoniazid and rifampin. MDR-TB escalates from drug resistant TB bacteria and/or from the consequences of mismanagement of the prescribed first-line medicines [4]. The key factor in the emergence of MDR-TB is the mismanagement of the desired course of therapy and/or a weak county-wide plan [5]. To deal with MDR-TB, second-line medicines such as para-aminosalicylic acid, amino glycosides, cycloserine, fluoroquinolones, thioamides, and cyclopeptides are employed. However, these second-line treatments may have adverse effects, the duration of treatment might be considerable, and their cost is about 100 times more than that of first-line therapies. MDR-TB can also develop resistance to second-line drugs thus making the situation more complicated.

2.3. XDR-TB

The worst circumstance occurs in the form of XDR-TB. In this type of TB, the bacteria develop resistance against isoniazid and rifampin along with essential second-line drugs that is, any of the fluoroquinolones and three injectable therapies, amikacin, kanamycin, and capreomycin. XDR-TB can also become resistant to other medicines, making the treatment more difficult. A person can also become the victim of XDR-TB by obtaining the XDR bacteria from a person already suffering from XDR-TB.

3. MACROPHAGES AND SURVIVAL MECHANISM OF TUBERCULOSIS BACTERIA IN MACROPHAGES

3.1. Macrophages

Macrophages (white blood cells) are the human defense against pathogens. Macrophages work equally well in unspecified action (innate immunity) and in assisting in the initiation of particular resistive action (adaptive immunity) of vertebrate species. Their mode of action is to take in and excrete leftover cells and pathogens after destroying them; they can work both as standing or moving units. Further, macrophages signal lymphocytes and other defensive units to take action against pathogens. Phagocyte units are specialized in assailing alien materials, contagious pathogens, and cancerous cells through a destructive mode of action [6]. Fig. 1 shows the detailed structure of a macrophage and a typical phagocytosis process.

3.2. Survival mechanisms of pathogenic Mycobacterium tuberculosis

The survival mechanisms of TB in macrophages Bacteria of the *Mycobacterium* genus have evolved several mechanisms to avoid the antagonistic surroundings of the macrophages (the chief host units for the TB) [7]. The mechanisms employed by the TB are thoroughly reviewed by Meena and Rajani [8]. Four of the mechanisms; inhibition of phagosome-lysosome fusion, inhibition of phagosomal acidification, protection against oxidative radicals, and the tryptophan aspartate-containing coat (TACO) protein on the phagosome wall are outlined. Inhibition of phagosome-lysosome fusion Growth inhibition and the killing of intracellular pathogens within the mononuclear phagocyte lineage host cell are considered to depend on phagosome-lysosome fusion [9]. *M. tuberculosis* is able to escape phagosome-lysosome fusion, hence avoids lysosomal killing. Inhibition of phagosomal acidification Vacuoles having *Mycobacterium avium* (type of mycobacterial infection) are not as acidic as nearby lysosomes [10, 11]. The lack of a vesicular proton-ATPase pump means that phagosomes within *M. avium* are not acidified. This inhibition of phagosomal acidification enables the bacterium to cope with the hostile environment of macrophages.

3.3. Protection against oxidative radicals

Highly reactive species such as oxygen and nitrogen radicals are produced in macrophages to destroy the intracellular bacteria. One of the proteins of the Erdman strain of *M. tuberculosis* cyclopropanates the double bonds of mycolic acid, resulting in a ten-time lower susceptibility to peroxides [12, 13].

3.4. TACO on the phagosome wall

Bacterial delivery to lysosomes is prevented by the TACO on the wall of phagosomes. TACO retained on the phagosome wall permits *Mycobacterium* spp. to escape the bactericidal action of macrophages [7].

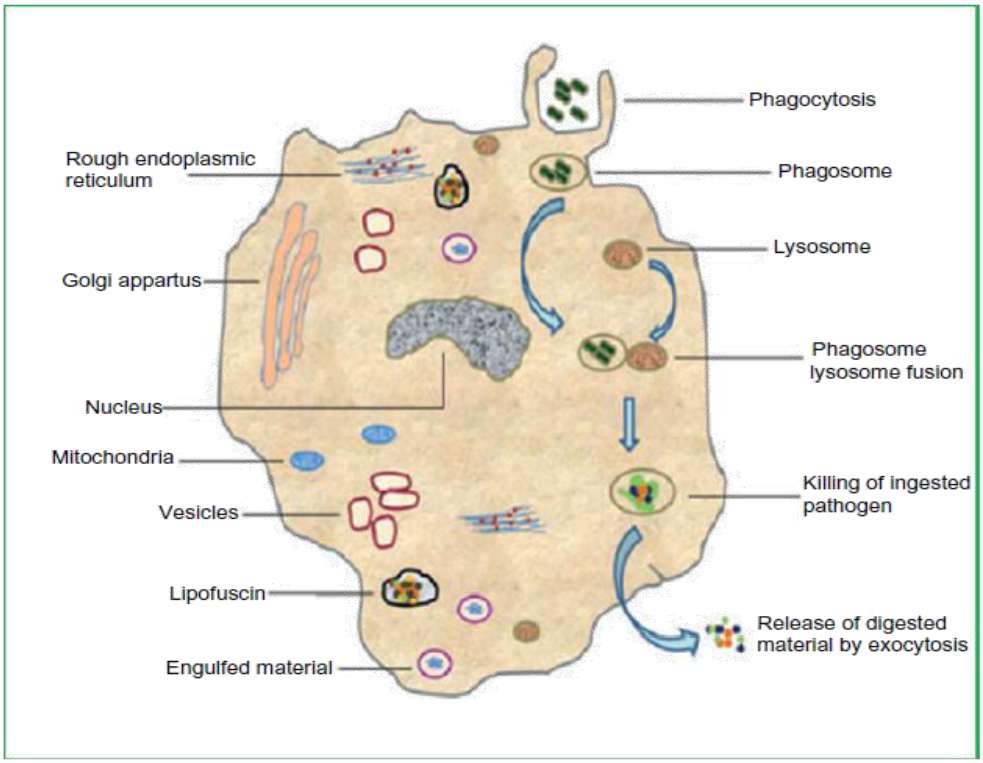

Fig. 1: Detailed structure of a macrophage showing a typical process of phagocytosis.

4. RESPONDING TO TB INTELLIGENTLY (WITH LIMITED CHEMOTHERAPY OPTIONS)

The key remedial tactic for dealing with the TB is to improve patient compliance by reducing drug toxicity and ensuring therapy is patient friendly [5]. DDSs seem to be the one of the best options in both these respects [8]. DDSs offer a tremendous way to avoid the adverse consequences associated with TB medicines, especially second-line drugs, by not exposing the drugs to healthy tissues. As already noted, many adverse effects are associated with prescribed TB medicines. A summary of the side effects of TB chemotherapy is given in table 2 [9-13]. Anaphylaxis, allergic reaction (e.g. exfoliative dermatitis, Steven-Johnson syndrome), severe gastritis with bleeding, hepatitis, and renal collapse are the life-threatening undesirable effects of the chemotherapy and in such circumstances treatment is stopped [14-17].

Patient outcomes must be improved by minimizing cytotoxicity to both the affected and healthy tissues and increasing patient compliance [15]. Thus, drug-delivery vehicles either have to target the place of infection or reduce the dosing frequency of drugs. There is an urgent need for uninterrupted efforts to develop drug-delivery vehicles that are patient friendly. Nanoscaled chemo-therapy would permit the uptake of medicine to be decreased, hence allow better execution of chemotherapy in TB [18].

4.1. DDSs for chemotherapy of tuberculosis

Currently, the focus of research is on the development of new anti-TB drugs; however, as previously noted, drug development is a lengthy process and no new anti-TB drug has been introduced in the last five decades. A more appropriate strategy would be to make more effective and deliberate use of the anti-TB drugs currently available. Therefore, DDSs should be the prime focus of TB research because they can enhance efficacy and minimize the side effects, dosage frequency, and treatment period.

Various approaches have been trialed by researchers in the area of sustained and targeted release of TB medicines, especially the use of nanoparticle DDSs for second-line anti-TB drugs. This review will now examine the advantages of various DDSs, especially nanoparticle DDSs, in the chemotherapy of tuberculosis and summarize the challenges in their implementation. Further, as nanotechnology has considerable potential in vaccination and other curative schemes against TB and other transferable pathogens, its benefits in the treatment of TB will also be explored [19, 20]. Sosnik et al [21] have thoroughly reviewed the application of

nanoscience and various nanoscaled DDSs in the treatment of tuberculosis, examining, among others, nanoemulsions, niosomes, nanodispersions, nanosuspensions, polymeric and non-polymeric nanoparticles, polymeric micelles, and other self-assembled structures such as dendrimers and liposomes. Further, Zhang et al [22] have reviewed polymeric nanoparticle DDSs, including solid lipid nanoparticles, dendrimers, and liposomes, for anti-microbial drugs. Their review is focused on recent advancements in nanocarriers designed for the delivery of antimicrobial agents. Pandey and Khuller [23] reviewed anti-TB drug carrying systems designed for pulmonary uses and have thoroughly reviewed the application of liposome-encapsulated anti-TB drugs, microparticles, and nanoparticles in the chemotherapy of pulmonary tuberculosis.

Table 1: Side effects of first-line antituberculosis drugs

Drug	Major adverse effects	Rare adverse effects
Isoniazid	Peripheral neuropathy, skin rash, hepatitis, sleepiness and lethargy	Convulsions, psychosis, arthralgia, anemia
Rifampin	Gastrointestinal abdominal pain, nausea, vomiting, hepatitis, generalized cutaneous reactions, thrombocytopenic purpura	Osteomalacia, pseudo-membranous colitis, pseudo-adrenal crisis, severe renal stoppage, hemolytic blood paucity
Pyrazinamide	Arthralgia, hepatitis, gastrointestinal problems, e.g., stomach upset, nausea, poor appetite and abdominal pain	Cutaneous reaction, sideroblastic anemia
Streptomycin	Vestibular and auditory nerve damage renal breakage, cutaneous allergic reaction	Pain, rash at injection site, numbness around the mouth and tingling soon after the injection
Thiacetazone	Skin rash that sometimes has mucosal involvement	Acute hepatic failure, exfoliative dermatitis

Table 2: Side effects of second-line antituberculosis drugs

Drug	Major adverse effects	Rare adverse effects
Kanamycin	Vestibular (vertigo) and auditory nerve damage	Cutaneous hypersensitivity
Amikacin	Vestibular damage (vertigo) and auditory nerve damage	Clinical renal failure
Ethionamide (prothionamide)	Gastrointestinal anorexia, nausea, diarrhea, abdominal pain, hepatotoxicity	Convulsions, mental symptoms, impotence, gynecomastia
Fluoroquinolones	Gastrointestinal anorexia, nausea, vomiting	Anxiety, dizziness, headache, convulsions, rupture of the Achilles tendon
Cycloserine	Dizziness, headache, depression, psychosis, convulsions	Suicide, generalized hypersensitivity, hepatitis
Para-aminosalicylic acid	Gastrointestinal anorexia, nausea, vomiting, hypersensitivity reactions (fever, rash, pruritus)	Hypothyroidism, hematological reactions

4.2. DDSs for pulmonary tuberculosis chemotherapy

Inhalation has received widespread recognition, as it is a simple, reproducible, and easy to use drug-delivery method. The lung tissues can be easily targeted by making use of the respiratory system. However, the slow release of medicine after respiration remains to be achieved, largely because of the dearth of appropriate equipment specially designed to deliver medicines to the lungs [23].

The majority of earlier research was focused on polymeric DDSs, especially those involving poly lactic-co-glycolic acid (PLGA) because it is readily available and safe. However, PLGA has limitations for use in the lungs. First, the drugs are released quickly and the remaining polymer takes weeks or months to degrade [24]. This results in an unwanted aggregation of polymer in the lungs with repeated doses. Secondly, the breakdown of PLGA microspheres causes an acidic hub that spoils pH-susceptible medicines, especially peptides and proteins [25]. In contrast, surface-corroding polymers, such as poly anhydrides, would not lower the pH, as their degraded fragments do not aggregate because of their high diffusion rates [26, 27]. Thirdly, although PLGA microspheres have a hydrophobic face that causes better particle delivery deeper into the lungs due to agglomeration of the microspheres by weak inter-particle forces; the hydrophobicity of the PLGA

surfaces causes protein adsorption that results in quick removal from the alveolar phagocytic cells [28]

In short, the application of polymeric systems for the sustained and targeted release of drugs in lungs is still at a nascent stage. Scientists have yet to design polymeric systems particularly for pulmonary use and they must overcome the limitations associated with the presently existing polymers, for example, PLGA [29-32].

4.3. DDSs for the targeted and measured delivery of anti-TB drugs

Many DDSs have been designed for the targeted and slow delivery of anti-TB drugs by adopting variety of different approaches. Some of these are discussed here.

4.4. Inhalable bulky porous particles (LPPs) of capreomycin

An MDR-TB patient's treatment may last up to 2 years because the bacteria have developed resistance to two of the most widely prescribed medicines, rifampin and isoniazid. Furthermore, for MDR-TB, other medicines are required and patients have to bear the extra burden of parental injection, mostly of capreomycin. The expected benefits of a simpler pulmonary delivery method are the elimination of administration by injection and improvement of patient compliance [33-35]. The capreomycin molecule consists of four active dynamic groups that are potentially active against microbes and the drug is known to be effective in combination with other suitable TB medicines for the elimination of MDR-TB from the lungs. However, much pain is associated with drugs given by injection, along with side effects such as thirst, anorexia, anemia, and, especially, nephrotoxicity, hearing damage, and vestibular splitting of cranial nerve VIII [28-30].

The normal dosage of capreomycin is 20 mg/kg of body weight/day (total dose, 1 g) for 2-4 months. The dose is injected intramuscularly, which is a major challenge to the administration of the drug for the specified time [31]. Although capreomycin is effective in MDR-TB, the adverse effects of the drug limit its therapeutic benefits. Targeted drug delivery can potentially sustain its remedial properties while diminishing exposure of the drug to healthy tissues, eliminating the possible adverse effects [36]. The utilization of aerosolized rifampin-PLGA microparticles in the chemotherapy of lungs TB has already been studied [37-40]. Low-thickness powders such as LPPs can be aerosolized, allowing the efficient delivery of medicine by simple inhalers. However, while LPPs are recognized for their powerful use in aerosolization, they neither aggregate quickly nor diffuse easily. LPPs also possess lower water solubility, which results in the discharge of drugs into the lungs for extended periods, since their large size inhibits macrophage phagocytes [40-46].

4.5. Compensation of DDSs in tuberculosis chemotherapy

Anti-TB drugs administered in traditional ways interact with healthy tissues before reaching the desired site requiring treatment, and thus harm healthy tissues because these tissues are exposed to the drugs for a longer period. DDSs do not allow unrelated sites to be exposed and deliver the drugs to the target place. Traditional treatment of TB involves patients having to take a large number of pills, up to eight at one time, for 3-24 months and, in case of MDR-TB, patients also have to have an intramuscular injection (eg, kanamycin, capreomycin, and amikacin) [47-50].

Although the development of novel anti-TB drugs remains the prime priority, development of DDSs with targeted and controlled-release properties has many potential benefits. Patient noncompliance, the most common reason for treatment failure, can be circumvented by the tendency of a delivery system to release the drug in a sustained manner. DDSs not only reduce dosing frequency but also the side effects related to second-line TB medicines and drug degradation. Furthermore, drug-delivery vehicles may be able to manage the strongest therapeutic effect of the drugs at their lower concentrations, as reported by Soto et al. [51]. Most importantly, such developed drug-delivery vehicles could also be utilized for new anti-TB drugs as they become available, to treat latent and active bacteria, curtailing the course of chemotherapy.

Inhaled chemotherapy may be more advantageous for the patients with pulmonary tuberculosis. Biocompatible drug-delivery vehicles have been designed with particle sizes that can be safely phagocytized. As MDR-TB cannot be effectively treated with most first-line TB antibiotics, matters are complicated because more side effects are associated with second-line anti-TB drugs. However, this can be overcome with drug-delivery vehicles that are able to deliver the drugs to desired places without cytotoxic effects on healthy tissues [52-54].

DDSs could also be used to solve the water solubility issues related to anti-TB drugs, such as rifampin, which is infamous for its poor water solubility. Encapsulation and/or loading efficiency can also be enhanced by the

adoption of various strategies. Zeta potential, the surface charge of material, can be varied using different methods and is a key factor to investigate in the delivery of drugs to the desired cells and tissues. In designing DDSs, researchers need to overcome the flaws associated with previously engineered DDSs [55-58].

5. CONCLUSION

TB still poses a devastating threat to the world and there is an urgent need to develop novel anti-TB drugs. DDSs offer a number of advantages over traditional methods of anti-TB drug administration and, once developed, such DDSs can be utilized for new anti-TB drugs. Some flaws are associated with the current DDSs that need to be overcome and dedication is required to take DDSs from *in vitro* and *in vivo* analyses to clinical trials.

Conflict of Interest

None declared

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