REVIEW ARTICLE

UPI JOURNAL OF CHEMICAL AND LIFE SCIENCES (UPI-JCLS)

ISSN: 2581-4648 (An International online Peer Reviewed Open Access Journal)

www.uniquepubinternational.com Published by Unique Pub International (UPI)

DRUG DELIVERY SYSTEM BASED ON NANOTECHNOLOGY METHOD FOR TUBERCULOSIS THERAPY

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Received: 24 Jan 2025 Revised: 22 Feb 2025 Accepted: 13 Mar 2025

Abstract

Tuberculosis (TB), derived from bacterium named Mycobacterium tuberculosis, has become one of the worst infectious and contagious illnesses in the world after HIV/AIDS. Long-term therapy, a high pill burden, lack of compliance, and strict management regimens are disadvantages which resulted in the extensively drug-resistant (XDR) along with multidrug- resistant (MDR) in the treatment of TB. One of the main thrust areas for the current scenario is the development of innovative intervention tools for early diagnosis and therapeutics towards Mycobacterium tuberculosis (MTB). This review discusses various nanotherapeutic agents that have been developed for MTB diagnostics, anti-TB drugs and vaccine. Undoubtedly, the concept of employing nanoparticles (NPs) has strong potential in this therapy and offers impressive outcomes to conquer the disease. Nanocarriers with different types were designed for drug delivery applications via various administration methods. Controlling and maintaining the drug release might be an example of the benefits of utilizing a drug-loaded NP in TB therapy over conventional drug therapy. Furthermore, the drug-encapsulated NP is able to lessen dosage regimen and can resolve the problems of insufficient compliance. Over the past decade, NPs were developed in both diagnostic and therapeutic methods, while on the other hand, the therapeutic system has increased. These "theragnostic" NPs were designed for nuclear imaging, optical imaging, ultrasound, imaging with magnetic resonance and the computed tomography, which includes both single-photon computed tomography and positron emission tomography. More specifically, the current manuscript focuses on the status of therapeutic and diagnostic approaches in the treatment of TB.

Keywords: tuberculosis, nanotherapeutic, theragnostic, diagnostic, therapeutic, nanoparticles, drug delivery System.

INTRODUCTION

Tuberculosis (TB) is possibly a contagious fatal illness that has a destructive effect on the human lungs. Mycobacterium tuberculosis, the TB-causing bacteria, can be spread through airborne droplets from one person to another by sneezes or coughs. In 1882, Robert Koch was awarded the Nobel Prize for this significant discovery. Mycobacterium tuberculosis (MTB) known as an intracellular pathogen and an acid-fast bacillus that has evolved a variety of survival mechanisms to resist of being destroyed by macrophages [1]. Almost a third of the world's population is infected with Mycobacterium tuberculosis (Mtb), and is therefore at risk of developing an active form of tuberculosis (TB) [2]. With an incidence of ten million cases and between one and two million deaths each year, Mtb was the second deadliest infectious agent in 2021 after SARS-CoV-2. Moreover, the recent coronavirus pandemic affected public health services in such a way that for the first time since 2005, the mortality rate associated with Mtb increased. Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), has plagued humankind since antiquity. Despite the remarkable advancement in medical science and therapeutics, tuberculosis (TB) still remains the primary factor of mortality and socioeconomic disaster for millions of people around the world. It has plagued humankind throughout known history and human prehistory. Tuberculosis is a deadly infectious disease caused by the bacteria Mycobacterium tuberculosis. The large contact surface area of airways is constructed by alveolar cells and goblet cells, whereas the main bronchiole cells consist of bronchial epithelial cells and Clara cells (mucus-producing cells). Alveolar type I epithelial cells and endothelial cells share a basement membrane. The air-blood barrier inside the lungs, with a size of 0.1-0.2 μm, is comprised of epithelial and endothelial tissue sharing the basement membrane. Although in the

European Region the TB incidence rate fell 15% between 2015 and 2018, the proportion of RR-/MDR-TB cases there (30%) is higher than that in all other regions (3.1–5.4%). Based on these, there is an increasing need for more effective therapies with less toxicity and shortened treatment duration. Nanotechnology offers several advantages to overcome the limitations of current TB therapy [3]. With the aid of this versatile approach, a sustained and targeted drug delivery can be achieved with the promise of an efficient pulmonary administration to further enhance treatment success. The preset progress report provides an overview of the potential use of nanotechnology-based drug delivery toward overcoming the challenges in TB treatment with more emphasis on pulmonary delivery. Nanomedicine eliminates side effects and toxicity of the drugs by delivering the medication to the target tissue in a particular way that avoids off-target release, whereas its nano-sized diameters increase the permeability and solubility of the drug loaded in the nanocarrier. Furthermore, this enhances the stability of drug by isolating it from other external factors [4]

TUBER CULOSIS:PATHOPYSIOLOG

Rethinking and optimizing the treatment of TB requires a general understanding of its physiopathology. Before focusing on the behavior of the pathogen at the cellular level, it is necessary to comprehend how Mtb operates at the level of the entire organism. During infection, the subject inhales bacilli, most of which are mechanically retained by mucus in the upper respiratory tract (usually with diameters higher than 5 m). The granuloma is a complex set of immune and inflammatory cells (such as macrophages, neutrophils, fibroblasts, T lymphocytes, B lymphocytes) that surrounds the infectious site and produces various cytokines and chemokines in order to maintain macrophage activation [5].

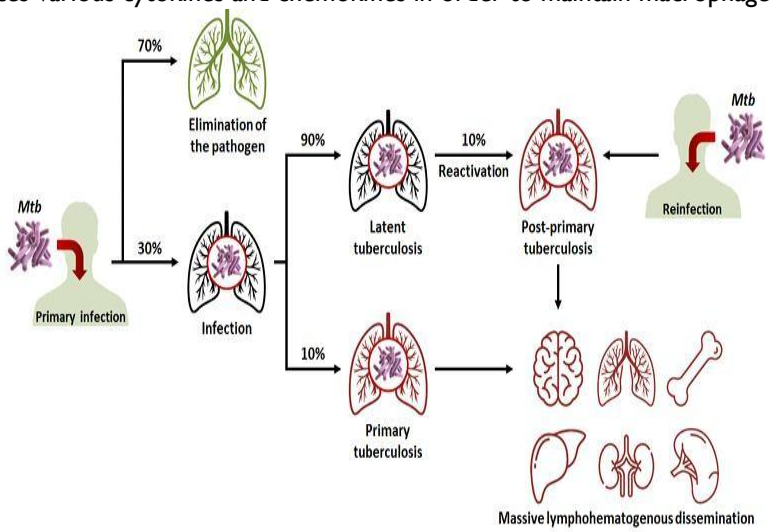

Figure 01. Evolution of the Different Clinical Stages of Tuberculosis (TB), From Primary Infection to Military TB.

DIFFERENT FORMS OF TB

There are two forms of TB, latent TB and active TB. In latent TB, bacteria remain dormant in body. This phase can last for much longer time. It is usually treated by taking one medicine for 9 months. And, in the active TB, bacteria multiply and spread in the body, thereby causing damage to the tissue [6].

Multidrug- Resistant Tuberculosis (MDR-TB)

This is onerous form of tuberculosis (TB) defined by resistance to at least two of the standard four drug anti-TB medicines (first-line antituberculosis drugs). Treatment of MDR-TB consists of second-line drugs. Many second-line drugs are lethal and have harsh side effects.Treatment for MDR-TB is administered for 2 years or more than that and involves daily injections. Without unique, simple, and inexpensive treatments for MDR-TB, this is next to impossible. WHO predicted that more than 2 million people would have developed MDR-TB between 2011 and 2015.

Extensively Drug-Resistance TB (XDR-TB)

XDR-TB poses a major risk to public health. This is more brutal form of MDR-TB and is characterized by resistance to any fluoroquinolone and at least one of the three injectable second- line drugs.[18] This makes this XDR-TB treatment extremely problematic. In the year 2006, XDR-TB outbroke in KwaZulu-Natal, South Africa; 52 out of 53 people who contracted the disease died within few months [7].

PATHOGENESIS AND IMMUNOLOGY OF TB

The first stage of tuberculosis is initiated with inhalation of droplets generated by a person with active tuberculosis. These droplets can remain for a longer time in the air. When inhaled, a single droplet may be enough to cause the disease. Most droplets end up in the upper respiratory tract, where the microbes are killed, but a few penetrate further down. The bacteria reach the alveoli in the lungs, where the alveolar macrophages phagocytose them. Several receptors are involved in the uptake process including mannose receptors, Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4), surfactant protein A receptors, CD14, scavenger receptors, complement receptors, and immunoglobulin receptors.

DIAGNOSIS

The first-line treatment of TB is so effective that, in the case of a non-resistant strain and a therapy followed to completion, the risk of relapse is only 5%–8%. Associated with INH, RFP reduces the duration of the therapy from eighteen to nine months. Taken for the first two months, PZA further reduces its duration by three months, leaving it at six months [8].

8. Nanotechnology Based Drug Delivery System Using nanocarriers in drug delivery is an emerging strategy in the combat against various diseases. The main advantages of nanocarrier systems over free drugs are enhanced bioavailabil -ity, protection of the entrapped drug from inactivation, sustained and controlled drug release, and the possibility of reducing the administered doses, and thus the related side effects and admin- istration frequency. To reach the reservoirs of MTB, a variety of nanocarriers have been developed, including polymeric nanoparticles, nano capsules, micelles, dendrimers, nanogels, liposomes, solid lipid nanoparticles, inorganic nanocarriers, etc [9].

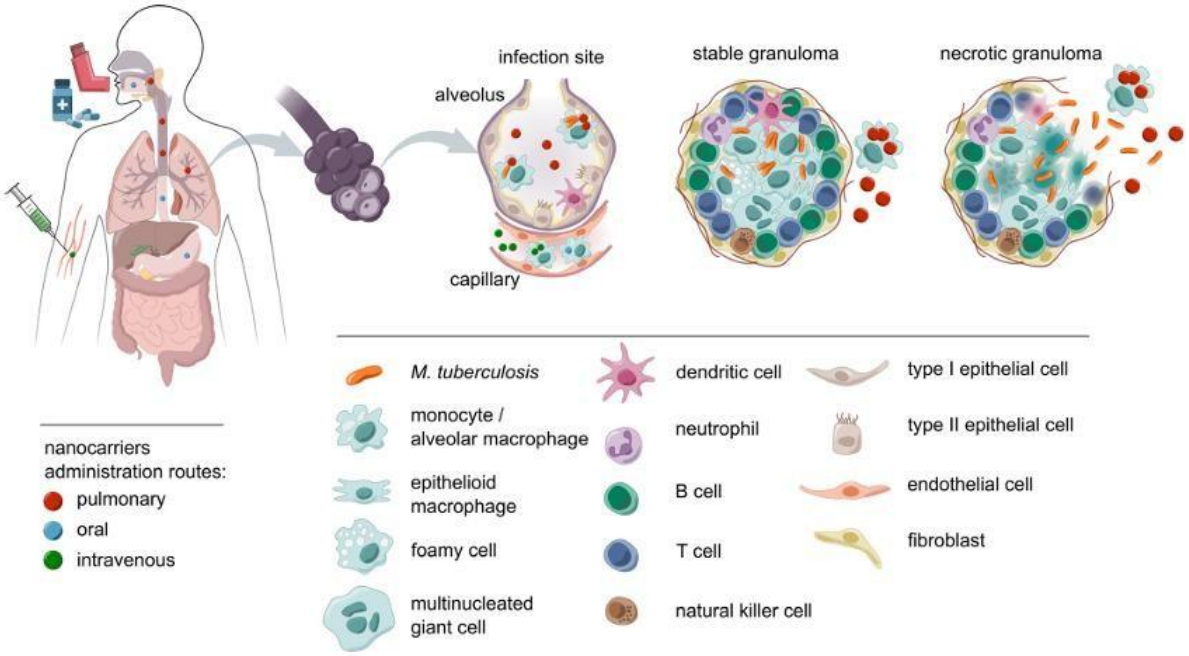

Figure 3. Targeting of alveolar macrophages and granulomas by nanocarriers Administered via different routes

THERAPIES BASED ON NANOTECHNOLOGY

Over the past few years, the budding use of nanotechnology-based therapy has been researched for replacing the administration of antibiotics or other drugs in the free form with an access using drugs that are encapsulated with nano particle. 10. Nanoparticles Classification of Nanoparticles Drug Delivery System for Treating TB. NPs have great potential to be applied as pulmonary delivery systems for the diagnosis and treatment of local respiratory diseases and may even exert systemic actions, such as blood coagulation and cardio vascular effects. Delivery of therapeutic drugs to target sites may be important for efficient treatment of tuberculosis, lung cancer, cystic fibrosis, and other acute and chronic respiratory infections. As early as 1654, an inhalation device was first designed by Bennet to produce opium vapor for cough treatment. The Food and Drug Administration (FDA) has already approved several materials as drug delivery systems, including liposomal, polymeric, dendrimers, inorganic and protein materials [10].

Liposomes

The application of liposomes as a drug delivery system has a significant impact on pharmacology. Liposomes are a class of lipid vesicles composed mainly of phospholipids and cholesterol. This colloidal form is comprised of a self-assembled lipid bilayer with amphiphilic domains, including an inner aqueous core and an outer shell of the lipid bilayer. Furthermore Furthermore, a previous study by Garbuzenko et al tested a variety of nanomaterials to select the best inhalation carrier for anticancer drugs, and revealed that compared with non-lipid-based carriers, lipid-based nanocarriers had advantages in terms of accumulation and retention time in the lungs [11].

Based on these advantages, liposomes became the earliest nanocarriers approved by the FDA in 1995, including liposome formulations of doxorubicin (DOX; Doxil®). Liposomal drug delivery systems have been applied to inflammatory respiratory diseases. For example, Konduri et al investigated the effect of liposomal budesonide on the treatment of asthma using a mouse model; the results revealed that this drug delivery system significantly improved lung inflammation and reduced the toxicity of inhaled steroid asthma drugs. Chen et al designed liposomes to encapsulate salbutamol sulfate (SBS) in aerosol form and demonstrated that the complexes exhibited longer anti-asthmatic effects than free SBS [12].

Solid lipid nanocarriers

SLNs are another type of lipid-based material, which are slightly different from liposomes in structure. SLNs may represent an alternative to traditional carrier systems due to their numerous advantages, including targeted drug delivery, controlled-release, high drug stability, high drug loading, encapsulation of hydrophilic and lipophilic drugs, low carrier toxicity, avoidance of organic solvents in production (such as high-pressure homogenization) and large-scale industrial production [13]. Their results showed that SLNs modified with the surfactants (mannose derivatives) could improve the absorption capacity of macrophages for their encapsulated drugs. A similar study was carried out by Nimje et al , which revealed that mannose-conjugated SLNs.

Polymeric nanocarriers

A polymer is a type of large molecule chemical compound, which is composed of numerous smaller homogeneous molecules. Polymers can be natural (albumin, gelatin, alginate, collagen, cyclodextrin and chitosan) or synthetic [poly-lactic-co-glycolic acid (PLGA), polyacry lates, polyethyleneimine (PEI), PEG, polyanhydrides and poly-l-lysine.The results The results showed that the nanomedicine had high drug loading and permeability, which could not only achieve high and persistent local drug concentration, but also decrease the drug dose to reduce side effects. Through in vitro and in vivo experiments, Kim et al revealed that the sustained-release inhalation system assembled by DOX and PLGA had high encapsulation efficiency and good nebulization ability, could effectively inhibit the growth of tumor cells and was suitable for the treatment of metastatic lung cancer [14].

Dendrimers

A dendrimer is a type of polymer nanostructure that is different from traditional polymers. It has a highly branched monodisperse three-dimensional structure. The multiple functional groups distributed on the surface of a dendrimer increase its versatility and biocompatibility as a nanocarrier.

INORGANIC NANOCARRIERS

There are several types of inorganic substances that have been used to synthesize NPs, including gold, silica, iron oxide, alumina and titanium dioxide. Inorganic NP carriers possess several advantages, such as high biocompatibility, high delivery efficiency, high stability, magnetic properties and resistance to microbial degradation. Despite these advantages, drug delivery systems using metal NPs as carriers still have some limitations. For example, when administered by intravenous injection, positively charged AuNPs are easily combined with negatively charged serum proteins in the blood and form aggregates [15].

PROTEIN NANOCARRIERS

Protein NPs include a large number of classes, such as endogenous protein carriers conjugated with drugs, engineered proteins and combined platforms that rely on protein or peptide motifs for targeting delivery. Protein NPs have many advantages, including high biocompatibility and solubility, biodegradability, modifiability, controlled-release properties and targeted drug delivery. At present, a large number of preclinical experiments based on protein nanocarriers have been reported in the field of respiratory diseases, particularly for respiratory infection (Table V).

Advantages and Disadvantages

To overcome the challenges and the side effect of conventional treatment, researchers have brought new novel formulation of nanomedicine which can provide effective therapeutics index. Inhalable nanoparticles are biodegradable and biocompatible, which contain high drug loading capacity this made them to enhanced mucosal cell adhesion, and improved drug delivery to the respiratory system for the treatment of (TB).[16] Although nanocarriers based drug delivery agents are achieved high drug loading, high stability, effective drug tolerability, reduce multidrug and extra drug resistance, controlled release, and site-specific delivery, the clinical phases are slow for the benefit of human. Physical and biological factors like pH, protein, phagocytic sequestration, enzyme, shear forces, renal clearance, and aggregation create hostile environments for nanocarriers [17].

Challenges and Future Perspectives

In recent decades, we have witnessed an extraordinary increase in our basic knowledge on TB. The sequencing of the first Mtb genome, in 1998, opened the way to molecular studies from the pathogen perspective, which would result eventually in the discovery of novel drug targets and the identification of virulence factors.[18] Diverse omics technologies have expanded vastly our current understanding of all stages of the disease, also from the host side. In fact, tuberculosis, i.e., the "white plague" has been a real pandemic for centuries. Oldest remains of people suffering from TB have been dated 9000 years ago.[19] Tuberculosis has a very big impact on developing nations. In this scenario, for the transition from experimental research to clinical trials requires an extensive understanding of the studied NPs' fate, both in vitro and in vivo [20].

CONCLUSION

Tuberculosis is among the most serious health issues worldwide with an annual rise in the number of patients. Nowadays, the conventional anti-tubercular therapeutic method needs high dosages of numerous drugs over a longer duration. This tends to result in drug-related detrimental effects or the development of MDR. Furthermore, the drugs currently in use have practical limits of solubility, stability, and penetration. Also, it may lead to resistance over time, resulting in relapse, and extend to peripheral body parts, which caused secondary TB. During the last 25 years, nanotechnology has emerged as a new strategy to improve drug delivery and efficiency of the actual treatments. However, many of the most successful nano formulations are focused on cancer treatment and only few of them are oriented for infectious diseases. Advancements in the nanoparticle-based drug delivery system represent a commercial, practical and most promising substitute for potential TB chemotherapy. Nanotechnology has become an important tool to overcome the defects of drugs, and to enable them to target specific cells or tissues passively or actively. The present review summarized the applications and advantages of NPs as drug delivery vehicles in respiratory diseases, such as lung cancer, asthma, chronic respiratory diseases, cystic fibrosis, tuberculosis and respiratory infection. Clearly, this topic attracts growing interest, as evidenced by the hundreds of publications dedicated to the subject. In constrast, the transition of the NPs to the clinical stage is not achieved yet. However, in the last twenty years, only four antitubercular drugs with novel mechanisms of action have been approved to treat MULTI DRUG RESISTANCE / EXTENSIVELT DRUG RESISTANCE TB. To achieve ground breaking progress and to make the pulmonary administration of nanoparticles feasible for noninvasive clinical trials, a multidisciplinary approach is necessary: nanotechnology, medicine and engineering must collaborate.

AUTHOR CONTRIBUTIONS

All authors are contributed equally

FINANCIAL SUPPORT:

None

DECLARATION OF COMPETING INTEREST

The Authors have no Conflicts of Interest to Declare.

ACKNOWLEDGEMENTS
None

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