IJPSR (2018), Volume 9, Issue 10 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 February, 2018; received in revised form, 21 April, 2018; accepted, 12 June, 2018; published 01 October, 2018

NANOPARTICULATE TECHNOLOGY IN THE TREATMENT OF TUBERCULOSIS: A REVIEW

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Keywords:

Tuberculosis, Nanotechnology, Delivery system, Anti tubercular drugs

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ABSTRACT: Tuberculosis (TB) is one of the second most deadly infectious disease which causes for morbidity as well as mortality. This communicable infectious disease is caused by *Mycobacterium tuberculosis*. It can produce silent, latent infection as well as progressive, active disease. Globally, 2 billion people are infected and roughly 2 million people die from tuberculosis each year. Despite for all the medical advancement, its resurgence among the developed world is a matter to be considered. Till date only BCG (*Bacillus* Calmette Guerian) vaccine is available which is ineffective against adult pulmonary TB, which is the common form of disease. The emergence of Multi Drug Resistant TB (MDR TB) and Extensively Dug Resistant TB (XDR TB) due to the misuse of anti-tubercular drugs is also a major concern. The traditional drug therapy involve long term and multiple drug dosing which leads to poor compliance among patients associated with severe side effects. Nanoparticle based treatment shows convincing and promising outcomes in the treatment of tuberculosis. This review discusses about nanoparticle technology which involves the encapsulation of antitubercular drugs as nanoparticles that leads to improved bioavailability, specific target site to the drug and circumvent the hepatotoxicity/ ototoxicity/ nephro toxicity/ ocular toxicity prevalent the first line chemotherapy.

INTRODUCTION: Tuberculosis (TB) is one of the fatal chronic infectious diseases caused by the strains of *Mycobacterium tuberculosis*, which is a small aerobic non motile bacillus. Despite all the medical advancement in therapeutics, it has been a burden for the past few decades. It is also called Koch's bacillus (named after the discovery of Robert Koch in 1882) [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(10).4109-16

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(10).4109-16

The TB epidemic is larger than previously estimated with a 10.4 million new incident TB cases worldwide in 2015, of which 5.9 million (54%) were among men, 3.5million (34%) among women and 1.0 million (10%) among children.

In 2015, there were an estimated 480000 new cases of multidrug resistant TB (MDR TB) and an additional 100000 people with rifampicin resistant TB [2]. *Mycobacterium* is an acid fast bacilli that divide very slowly in about 16 - 20 h compared to other organisms. It primarily attacks lungs (pulmonary TB), it can affect other parts of body like kidney, lymphatic system, central nervous system (meningitis), circulatory system (military TB), genitourinary system, joints and bones.

The conventional treatment of TB involves using first line agents (isoniazid INH, rifampin RIF, pyrazinamide PZA, ethambutol EMB and streptomycin) for a period of 6 months, with follow up to 1 year while the second line agents (kanamycin, amikacin, ethionamide, cycloserine) are often given as injections. These drugs when administered, majority of molecule do not reach their specific sites and accumulate in the body for a long time. Due to this long period of treatment, patient will develop multiple drug resistance, low bioavailability, low therapeutic index and severe side effects such as hepatotoxicity/ nephrotoxicity/ ototoxicity/ocular toxicity that has led to the emergence of MDR (Multiple Drug Resistant TB) and XDR TB (Extensive Drug Resistant TB).

One of the major problems is noncompliance to prescribed regimens, primarily because treatment of TB involves continuous, frequent multiple-drug dosing. Adherence to treatment and the outcome of therapy could be improved with the introduction of long-duration drug formulations releasing the drugs in a slow and sustained manner, which would allow reduction in frequency and dosing numbers. So we need a system that can improve the therapeutic challenges of the conventional therapy. Nanoparticle drug delivery system represents an ideal method to overcome the failure of the initial therapy, it involves encapsulating the anti-tubercular drug for eliciting controlled, sustained and more profound effect and circumvent the toxicities prevalent with first line chemotherapy [3]. The primary goals for research of nano-bio-technologies in drug delivery include:

- More specific drug targeting and delivery,
- Reduction in toxicity while maintaining therapeutic effects,
- Greater safety and biocompatibility, and
- Faster development of new safe medicines [4].

The use of different nanotechnology-based drug delivery systems such as Polymeric Nanoparticles (PN), Solid Lipid Nanoparticles (SLNs), Liquid Crystal (LC) systems, Liposomes (LIP), Micro-emulsions (MEs), Nanomicelles (NAs) and metal-based nanoparticles (gold nano particles, silver nanoparticles, iron oxide nanoparticles) is an interesting approach to improve on the most desirable properties of a formulation [3].

What is Tuberculosis? Tuberculosis caused by mycobacterium tuberculosis is a chronic infectious disease affecting as a killer worldwide. Mycobacterium, from the Greek “mycos”, due to their waxy appearance of their cell walls. It is the second most deadly disease after Human Immune Deficiency Virus (HIV). It is a gram positive organism that grows only inside the cells of host. It mainly attacks the lung causing pulmonary TB. Also it can infest other parts of body such as kidney, lymphatic system, central nervous system, circulatory system, bones and joints. The disease is spread when people who are sick with TB expel bacteria in to the air, for example by coughing.

Epidemiology: In spite of the major advancement in therapeutics, tuberculosis appears to be a fatal disease in countries like Africa, Latin America and Asia. More than two billion people (about one third of the population) are estimated to be affected with tuberculosis. The TB epidemic is larger than previously estimated with a 10.4 million new incident TB cases worldwide in 2015, of which 5.9 million (54%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. In 2015, there were an estimated 480000 new cases of multidrug resistant TB (MDR TB) and an additional 100000 people with rifampicin resistant TB. Now according to the survey TB remains as one of the top 10 causes of death worldwide in 2015 [2].

Aetiology: The main risk factors for TB include malnutrition, poverty, other debilitating disease such as diabetes, alcoholism and immuno-compromised patients (renal failure, cancer, immunocomprimised drugs). HIV infected patients has the more incidence of getting affected by TB. The risk accounts of 10% or more.

Mode of Transmission: Human beings acquire infection with tubercle bacilli by one of the following routes:

1. Inhalation of organisms present in fresh cough droplets or in dried sputum from an open case of pulmonary tuberculosis.
2. Ingestion of the organisms leads to development of tonsillar or intestinal tuberculosis. This mode of infection of human tubercle bacilli is from self-swallowing of infected sputum of an open case of pulmonary

tuberculosis, or ingestion of bovine tubercle bacilli from milk of diseased cows.

3. Inoculation of the organisms into the skin may rarely occur from infected postmortem tissue.
4. Transplacental route results in development of congenital tuberculosis in foetus from infected mother and is a rare mode of transmission [1].

Pathophysiology: The sequences of events which take place when tubercle bacilli are introduced into the tissue are as under:

1. When the tubercle bacilli are ingested, the bacilli are lodged in pulmonary capillaries where an initial response of neutrophils is evoked which are rapidly destroyed by the organisms.
2. After about 12 h, there is progressive infiltration by macrophages. This is due to coating of tubercle bacilli with serum complement factors C2a and C3b which act as opsonins and attract the macrophages. Macrophages dominate the picture throughout the remaining life of the lesions. If the tubercle bacilli are, however, inhaled into the lung alveoli, macrophages predominate the picture from the beginning.
3. The macrophages start phagocytosing the tubercle bacilli and either kill the bacteria or die away themselves. In the latter case, they further proliferate locally as well as there is increased recruitment of macrophages from blood monocytes.
4. As a part of body's immune response, T and B cells are activated. Activated CD^{4+}T cells develop the cell-mediated delayed type hypersensitivity reaction, while B cells result in formation of antibodies which play no role in body's defence against tubercle bacilli.
5. In 2-3 days, the macrophages undergo structural changes as a result of immune mechanisms-the cytoplasm becomes pale and eosinophilic and their nuclei become elongated and vesicular. These modified macrophages resemble epithelial cells and are called epithelioid cells.
6. The epithelioid cells in time aggregate into tight clusters or granulomas. Release of cytokines in response to sensitised CD^{4+}T cells and some constituents of mycobacterial cell wall play a role in formation of granuloma.
7. Some of the macrophages form multinucleated giant cells by fusion of adjacent cells. The giant cells may be Langhans' type having peripherally arranged nuclei in the form of horseshoe or ring, or clustered at the two poles of the giant cell; or they may be foreign body type having centrally-placed nuclei.
8. Around the mass of epithelioid cells and giant cells is a zone of lymphocytes, plasma cells and fibroblasts. The lesion at this stage is called hard tubercle due to absence of central necrosis.
9. Within 10-14 days, the centre of the cellular mass begins to undergo caseation necrosis, characterised by cheesy appearance and high lipid content. This stage is called soft tubercle which is the hallmark of tuberculous lesions. The development of caseation necrosis is possibly due to interaction of mycobacteria with activated T cells (CD^{4+} helper T cells *via* IFN-γ and CD^{8+} suppressor T cells directly) as well as by direct toxicity of mycobacteria on macrophages. Microscopically, caseation necrosis is structureless, eosinophilic and granular material with nuclear debris.
10. The soft tubercle which is a fully-developed granuloma with caseous centre does not favour rapid proliferation of tubercle bacilli. Acid-fast bacilli are difficult to find in these lesions and may be demonstrated at the margins of recent necrotic foci and in the walls of the cavities [1].

Clinical Presentation:

1. Patients typically present with weight loss, fatigue, a productive cough, fever and night sweats, frank hemoptysis.
2. Physical examination shows dullness to chest percussion, rales, and increased vocal fremitus on auscultation.
3. Laboratory tests show moderate elevations in white blood cell count with lymphocyte predominance.
4. Chest radiograph shows patchy or nodular infiltrates in the apical area of upper lobes or the superior segment of lower lobes.
5. Cavitation that may show air - fluid levels as the infection progress.

Diagnosis:

Mantoux Test: It is a purified protein test using tuberculin protein derivative. An amount of 5

tuberculin units is injected intradermally and it should produce a raised tender, red wheal within 48 to 72 h. The area of induration of 5 mm suggests a positive test. To finalize the diagnosis of active TB disease, *M. tuberculosis* must be detected and isolated from sputum, gastric aspirate, spinal fluid, urine, or tissue biopsy, depending on the site of infection.

Quantiferon TB Gold Test: In a latent infected individual there occurs the release of INF-gamma which accounts a positive test whereas the test will be negative in blood samples taken from uninfected individual. T cells stimulate release of interferon-γ. The Quantiferon TB Gold and Quantiferon-TB Gold In-Tube tests measure the interferon-γ concentrations released using an enzyme-linked immunosorbent assay [1].

Treatment:

Conventional Drug Therapy: Drug therapy is the corner stone of patients affected with TB. It features on relieving the signs and symptoms associated with the disease, providing patient adherence to the regimen and complete cure of the disease. To accomplish these goals, treatment must be tailored to each patient's clinical and social circumstances to ensure adherence to and completion of the treatment regimen (patient centered care). Effective treatment of TB requires a substantial period (minimum 6 months) of intensive drug therapy with at least two active bactericidal drugs. Optimization of this initial phase of treatment prevents emergence of resistance and ensures the success of TB therapy [5].

First Line Drugs: Current guidelines recommend four drugs for the initial 8-week treatment phase: isoniazid, rifampin, pyrazinamide and ethambutol. Because patients must be treated for a long time, Directly Observed Therapy (DOT) is the preferred core management strategy to ensure adherence.

Second Line Drugs: The second-line drugs used for the treatment of TB are aminoglycosides such as Amikacin (AMK) and Knamycin (KM), polypeptides such as capreomycin, viomycin, enviomycin, fluroquinolones such as Ciprofloxacin (CIP), levofloxacin, Moxifloxacin (MXF), thioamides such as ethionamide, prothioamide and cycloserine.

Third Line Drugs: The third-line drugs for treating TB include rifabutin, linezolid (LZD), thioidazine, arginine, vitamin D, macrolides such as Clarithromycin (CLR) and thioacetazone (T) [6].

TABLE 1: DRUG REGIMEN FOR CULTURE POSITIVE TUBERCULOSIS CAUSED BY SUSCEPTIBLE ORGANISMS [7]

	Initial Phase		Continuation Phase	
Regimen	**Drugs**	**Intervals and Doses**	**Drugs**	**Intervals and Doses**
1	Isoniazid, rifampin, pyrazanamide, ethambutol	Seven days per week for 56 doses (8weeks) or 5 days per week for 40 doses (8 weeks)	Isoniazid, rifampin	seven days per week for 126 doses (18 weeks) or 5 days per week for 90 doses (18 weeks)
			Isoniazid, rifampin	twice weekly for 36 doses (18 weeks)
			Isoniazid, rifapentine	once weekly for 18 doses 18 weeks
2	Isoniazid, rifampin, pyrazanamide, ethambutol	Seven days per week for 14 doses (2 weeks) then twice weekly for 12 doses or 5 days per week for 10 doses then twice weekly for 12 doses	Isoniazid, rifampin,	Twice weekly for 36 doses (18 weeks)
			Isoniazid, rifapentine	Once weekly for 18 doses 18 weeks
3	Isoniazid, rifampin, Pyrazanamide, ethambutol	Three times weekly for 24 doses (8 weeks)	Isoniazid, rifampin,	Three times weekly for 54 doses (18 weeks)
4	Isoniazid, rifampin, ethambutol	Seven days per week for 56 doses (8 weeks) or 5 days per week for 40 doses (8 weeks)	Isoniazid, rifampin,	7 days per week for 217 doses or 5 days per week for 155 doses
			Isoniazid, rifampin,	Twice weekly for 62 doses (31 weeks)

Disadvantages of Conventional Drug Therapy:

- The conventional treatment involves a long term therapy that may result in less patient compliance and also multiple side effects associated with first line chemotherapy such as hepatotoxixity / nephro toxicity/ocular toxicity/ ototoxicity.
- The inappropriate use of medication due to the long term treatment has lead to the development of multiple drug resistant tuberculosis (MDR - TB) and extensively drug resistant tuberculosis (XDR- TB).
- The preferred route of administration in TB is oral that accounts for the pharmacokinetic problems such as low bioavailability, inadequate therapeutic index.

Why Nanoparticle Technology? Nanoparticle is a broad term that refers to a colloidal particle with a size of less than 1 micron (<1µm). Nanoparticle based drug delivery systems have considerable potential for treatment of TB. This delivery system having several advantages like high stability, high loading capacity, feasibility of incorporation of both hydrophilic and hydrophobic drugs, and feasibility of variable routes of administration, and prolonged release from the matrix.

These advantages of nanoparticles enable improvement of drug solubility, bioavailability, reduction of the dosing frequency, high targeting, and may resolve the problem of nonadherence to prescribed therapy, which is one of the major obstacles in the control of TB epidemics.

Advantages of Nanoparticulate Drug Delivery:

- The size and versatility of the nanoparticles makes the drug administration better over standard techniques.
- Nanocapsules have been commonly shown to increase efficacy of the administered drugs, reduce degradation in the bowels, and increase uptake and bioavailability
- Upon administration, nanoparticles are directly supplied to the bloodstream with all ATDs, in effect resulting in absolute bioavailability.
- Nanopaticles can use multiple synergistic paths to enhance the antimicrobial activity and overcome the antibiotic resistance.

Types of Nanocarriers: Nanoparticles comprise biocompatible and biodegradable materials such as polymers, which can be:

- Natural: *e.g*., liposomes, alginic acid , chitosan, gelatin and albumin
- Synthetic: *e.g*., poly-lactide-co-glcolide (PLG) polylactides and polyalkylcyanoacrylates
- Solid lipids.

Nanoparticle Drug Delivery Systems: Nano-particles are taken up more efficiently by cells than larger molecules which make them a promising delivery system. These carriers are adapted to enable oral drug delivery of anti tubercular drugs. Oral administration is possible due to the stability, controlled, slow, and persistent drug release from the matrix. PLG is a copolymer of lactic acid and glycolic acid that is completely biodegradable and biocompatible. Three leading anti tubercular drugs, namely, rifampin (RIF), isoniazid (INH), and pyrazinamide (PYZ), is used for the tuberculosis treatment.

A study was conducted by Pandey and his colleagues which demonstrated the efficacy of nano particulate drug delivery of anti tubercular drugs. These drugs were prepared by solvent evaporation method and by double emulsion process, which were encapsulated by PLG nano particles. Drug levels were maintained above the least inhibitory concentration (MIC90) in mice after a single oral administration of drug-loaded PLG nanoparticless for 6 to 9 days in the plasma. Though free drugs were vacant from plasma within 12-24 h following the oral administration complete bacterial clearance from the organs was observed when TB infected mice were treated with the nanoparticle-bound drugs (5 oral doses every 10^{th} day). With con-ventional therapy the same effect can be observed only after the administration of 46 doses [4].

Ligand - Conjugated Oral - Antitubercular Nano-medicine: Polymeric nanoparticles act as bioadhesive in gastrointestinal tract. PLG nano-medicine was further improved by the addition of bioadhesive ligand. Lectins, a mucosal ligand that have been shown to improve the adhesion of nanoparticle to the mucosal surface which increases the absorption associated with drugs and its bioavailability.

Wheat germ agglutinin's receptors are distributed on intestinal and alveolar epithelium, thus making it useful for oral as well as aerosol drug delivery, and its covalent attachment to PLG has been shown to boost the efficacy of anti-TB drugs.

Upon oral/aerosol administration of wheat germ agglutinin-coated PLG nanoparticles, it showed prolonged plasma levels of 6 to 7 days for RIF and 13 to 14 days for INH and PYZ as compared to uncoated PLG-Nanoparticles (4-6 days for RIF and 8-9 days for INH and PYZ). Three oral/nebulized doses of these lectin-coated nanoparticles every 14 days resulted in complete bacterial clearance. All three drugs were present in lungs, liver, and spleen for 15 days. It also has extensive application in drug delivery due to its low immunogenicity.

These nanoparticles lasted for long time because of the fact that lectins improve prolonged adhesion of the particles to the intestinal shell to permit an increase in the time interval for absorption and also increase in the concentration gradient between serosal and luminal sides of the membrane [4].

Liposome-based Drug Delivery Systems: Liposomes are miniature closed vesicles consisting of phospholipid bilayer enfolding an aqueous section. When administered, phagocytic cells promptly recognize these carriers and vacant them from the blood stream. Vigorous take-up by alveolar macrophages is effective against intra-cellular pathogens which are the major advantage of using liposomes. As liposomes are susceptible to intestinal lipases, they must be administered by either respiratory means or intravenous route. Nonspecific uptake by Mononuclear Phagocyte System (MPS) of liver and spleen can be reduced by the inclusion of PEG in the liposomal formulations.

Upon administering TB infected mice twice a week for 6 weeks; it was observed that liposomes encapsulated drugs (rifampicin or isoniazid alone) were more powerful in clearing mycobacterial infection when compared to the free drugs. Dose can be reduced to one weekly administration for 6 weeks when these two front-line Anti tubercular drugs (ATDs) were coadministered in liposomes. As per histopathological examination, no hepato-toxicity was reported and was supported by levels of serum albumin, alanine aminotransferase, and alkaline phosphatise [8].

Microemulsions as Potential Anti-TB Drug Delivery Systems: Microemulsion is a system of water, oil and an amphiphile (surfactant and co-surfactant) which is a single optically isotropic and thermodynamically stable liquid solution.

Microemulsionsis used because of their thermodynamic stability, high diffusion and absorption rates, ease of preparation, and high solubility. They improve the drug bioavailability, resistance against enzymatic hydrolysis, and reduced toxicity. The droplets of microemulsions have small particle size ranging 10 - 100 nm and high thermodynamic stability. There are three different types of microemulsions:

(a) Oil-in-water (o/w),
(b) Bicontinuous,
(c) Water-in-oil (w/o) microemulsion [8].

Niosomes-Based Anti-TB Drug Delivery System: Niosomes are thermodynamically stable liposomes. They are formed by the self-assembly of nonionic surfactants and hydrating mixtures of cholesterol in aqueous medium and results in the production of multilamellar systems, unilamellar systems, and polyhedral structures. The bilayer system consists of uncharged single-chain nonionic surface-active agents. The molecular size ranges 10 nm to 100 nm.

Niosomes have following advantages:

- Biodegradability
- Biocompatibility
- Chemical stability
- Low production cost
- Easy storage and handling
- Low toxicity [8]

Other Drug Delivery Systems:

Pulmonary Delivery of Anti-Tubercular Drug Nanomedicine: Pulmonary TB is the most ubiquitous form of the disease, and the respiratory path represents a unique means of delivering ATDs directly to the lungs. Reduction of systemic toxicity and accomplishing higher drug concentration at the chief site of infection are the promising advantages of direct delivery of drug to the lungs. Inhalable Nanoparticles possess an enhanced ability of

mucosal adherence, particle delivery, and net drug delivery to the lungs.

Intravenous Delivery of ATD Nanomedicine: There are three injectable routes of drug delivery. Among these, intravenous administration of drugs results in immediate availability of all the drug molecules and increases bioavailability. Other routes like subcutaneous and intramuscular routes also provide similar bioavailability as compared to intravenous route.

A single subcutaneous injection of PLG nano-particles loaded with RMP, INH, and PZA resulted in sustained therapeutic drug levels in plasma for 32 days and in lungs or spleen for 36 days. This produced complete sterilization of organs of TB infected mice and demonstrated better therapeutic efficacy as compared with daily oral free drugs (35 doses). This demonstrates the better efficacy of nanoparticles compared to microparticles. Nano-particles have easy intracapillary passage and this is followed by efficient cellular uptake. Then they are endocytosed by the macrophages and the circulating monocytes. Microparticles with diameter of more than 1 μm cannot be administered via intravascular route; however, nanoparticles are small enough to pass through.

Clofazimine is an anti-TB drug for mycobacterial infection but the use of this drug was limited because of its less solubility. To overcome this problem, nanoparticulate drug delivery system was used. Clofazimine was formulated as a nano-suspension (particle size, 385 nm). Upon intra-venous administration of this formulation, a significant reduction of colony-forming unit count in the liver, spleen, and lungs of mice infected with *M. avium* was observed [4].

Major Obstacles to Nanoparticulate Technology: However, there are many obstacles that are yet needed to be solved as a disease of poverty and insufficient health structures these nanoparticulate drug delivery cannot be implemented lack of human trials is another major obstacle. Moreover, the injectables route of administration needs more medical supervision and medical professionals. These nanoparticulate formulations should be stored under specified storage condition which is unfeasibile in low income conditions [9].

CONCLUSION: The development of nano-particulate technology and nanoparticulate drug delivery systems for tuberculosis treatment is a cost effective and promising tool. The disadvantages associated with the conventional therapy can be easily removed by nanoparticulate technology; it takes current chemotherapy and utilizes it more efficaciously.

Further, extensive studies on nano-particulate technology can help in the antimicrobial drug delivery to the infected sites and improve the treatment of life threatening diseases. Their advantages like improvement in bioavailability, reduction in dosing frequency remains to be a strong ground for the better management of the diseases.

Another major advantage is its ability to use different routes for the drug delivery and there by achieving maximum therapeutic activity of drug. These advantages will likely improve completion rates by reducing the burden on both the patient and to health infrastructure itself, such as making the directly observed treatment short course (DOTS) program more manageable and affordable [10]. By using readily available technology, nanoparticle delivery of ATDs provides a logical, cheap, and attractive solution.

ACKNOWLEDGEMENT: First and foremost we thank the Almighty. We extend our sincere thanks to the principal of our institution Dr. Elssey Abraham and Mrs. Soniya Scaria, guide of this review article for providing necessary information and support in completing the review. We would also like to express our gratitude towards our parents for their support and encouragement.

CONFLICT OF INTEREST: The authors declare that there are no competing interests.

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How to cite this article:
Varghese S, Anil A, Scaria S and Abraham E: Nanoparticulate technology in the treatment of tuberculosis: A Review. Int J Pharm Sci & Res 2018; 9(10): 4109-16. doi: 10.13040/IJPSR.0975-8232.9(10).4109-16.