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Application of Nanomedicine Technology for treatment of Tuberculosis: An overview

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Abstract:

Introduction: Tuberculosis (TB), the second most serious infectious disease after AIDS that not only attacks lungs, but also spine and brain. TB is an infectious disease caused by *Mycobacterium tuberculosis*. Worldwide, 2 billion people are diagnosed with TB and approximately 2 million patients die from it. Traditionally long-term therapy involving various medications is used to cure TB, leading to several adverse effects, poor compliance to patient and drug resistance. The pathogens of TB located in the intracellular section of the cells, which eventually results in further impediment to effective treatment. Therefore, better and more efficient therapies for such diseases are required.

Methods: The prospects of Nanomedicine (NM) for successful TB treatment are discussed in this review article. To fulfill the purpose, we searched various indexed literature using systematic and organized criteria. Standard criteria were used to assess the accuracy and characteristics of selected papers.

Results: For chronic infectious diseases like TB, nanoparticles (NP)-based technology has shown successful therapy and positive results. Nanocarriers such as NP, liposomes, niosomes, and microspheres give the ability to develop noval therapeutic and diagnostic strategies due to their specific size-dependent properties. In addition to the advantage of providing control release of medications, the other advantages of the nanocarriers comprises the possibility of using different routes of administration, decrease in drug dosage and side effects, reduced chances of drug incompatibility, and effective drug-resistant (DR) treatment. . According to available literature and proprietary studies, NM drug delivery can enhance TB chemotherapy providing benefits such as targeted drug delivery to a particular organ as well as sustained and controlled drug release.

Conclusion: The application of NM mediated technologies could aid in developing improved, efficacious or alternative chemotherapies for TB diseases.

Keywords: Nanoparticle, Tuberculosis, Nanocarrier, Nanomedicine

1. Introduction:

TB is a infectious and communicable illness caused by the strains of Mycobacterium tuberculosis (MT), also known as Koch bacillus (named after inventor Robert Koch in 1882) [1, 2]. MT survive and replicating within human alveolar macrophages and affecting other organs. In 2015, there were 10.4 million new TB cases globally, including 5.9 million men, 3.5 million women, and 1.0 million children's [3, 4].

In 2015, there were approximately 480000 new reports of multidrug resistant TB (MDR TB) and an additional 100000 reports of RF resistant TB. In comparison to other species, Mycobacterium divides very slowly in about 16 to 20 hours [5]. It mainly affect lungs (pulmonary TB), but it can also affect other parts of body like kidney, central nervous system (meningitis), circulatory system (military TB), urinary system and joints [6].

A six-month regimen of antibiotics, consisting of four separate antibiotics, is the standard medication for tuberculosis: rifampicin (RF), isoniazid (INZ), pyrazinamide (PZA) and ethambutol (EB), with follow up to 1 year (Table 1). While second-line antibiotics i.e. kanamycin, amikacin, ethionamide and cycloserine are administered as injections [7, 8]. When these drugs are given, the majority of the drug molecules do not reached to their target sites and deposite in the body for an extended period. The patient develops multiple drug resistance and poor bioavailability because of the prolonged period of treatment, lower therapeutic index and many adverse effects such as hepatotoxicity/ ocular toxicity / ototoxicity/ / nephrotoxicity that has contributed to the advent of MDR (Multiple Drug Resistant TB) and XDR TB (Extensive Drug Resistant TB) [9].

Table 1: Tradition drug therapy for treatment of TB

Initial phase			**Continuous phase**	
Drug Therapy	Drug	Dose Regime	Drugs	Dose regime
1	INZ, RF, PYZ, EB	7 Days per week 56 doses (8 weeks)	INZ, RF	7 days per week for 126 doses (18 weeks)
2	INZ, RF, PYZ, EB	7 days per week 14 doses (2 weeks), after that twice weekly for 12 doses	INZ, RF	2 times a week for 36 doses (18 weeks)
3	INZ, RF, PYZ, EB	3 times a week for 24 doses (8 weeks)	INZ, RF	3 times a week for 54 doses (18 weeks)
4	INZ, RF, EB	7 days per week for 56 doses (8 weeks)	INZ, RF	7 days per week for 217 doses

Disadvantages of Conventional Drug Treatment [10]

- The traditional drug therapy requires prolonged treatment that results in poor compliance to patient and various adverse reactions. The improper use of drugs due to the prolonged treatment has leads to the XDR-TB and MDR-TB.
- Oral administration is the favourate route of administration in TB, which can leads to pharmacokinetic issues such as poor bioavailability and a low therapeutic index.

NP represents a viable alternative to conquer the failure of the first line therapy. It involves encapsulating the anti- TB drug in order to achieve a controlled, long-lasting, and more profound effect while avoiding the side effects associated with first-line treatment. The primary goals for research of Nanotechnology (NT) include:

- Effective drug targeting,
- Lower toxicity with better therapeutic impact,
- Improved protection and biocompatibility
- Fast development of noval and safe medicines

The use of different NT-based drug delivery techniques (Fig.1) such as Polymeric Nanoparticles), Liposomes , systems, Solid Lipid Nanoparticles, Liquid Crystal and Nanomicelles, Micro-emulsions is best approach to improve on the most useful attributes of a formulation [10].

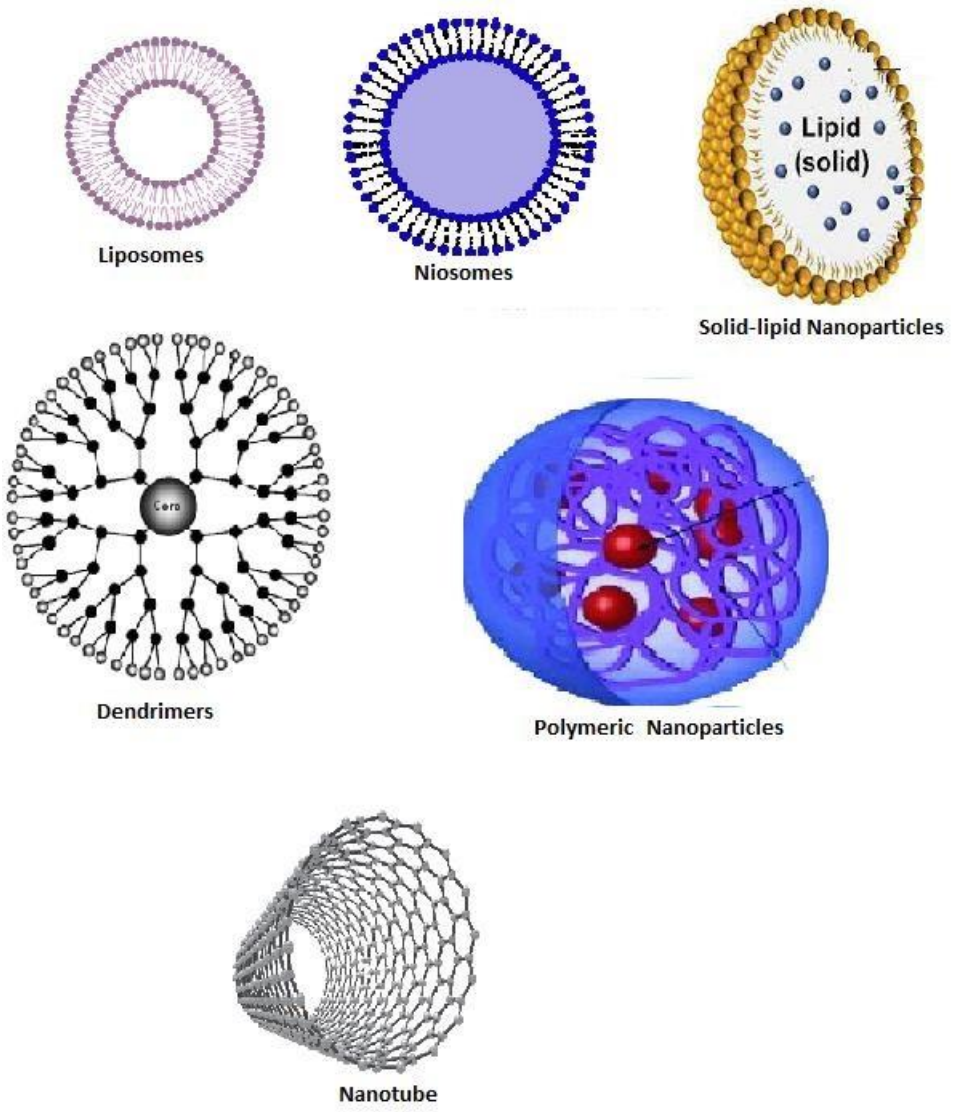

Fig 1: Various types of Nanotechnology dosage form.

2. Nanomedicine as an Emerging Therapeutic Approach for treatment of TB:

NT is a broad term that refers to any drug delivery system having a colloidal particle size of below 1 micron (<1µm) [11].

NP are more easily absorbed by body cells than the big molecules, making them a promising delivery system for TB. These carriers are adapted to provide controlled and sustained drug delivery from the matrix. Several approaches for preparing and characterization of NP have been explored in numerous articles [12, 13].

Advantages of NP for TB treatment:

(1) It provided higher consistency for longer period.
(2) More than one drugs can be encapsulated in the matrix due to its high carrier ability.
(3) As compared to traditional medications, there are decreased side effects.
(4) Higher bioavailability
(5) The viability of various route of administration
(6) Increased compliance of patient

Nanomedicine tends to be one of the most effective ways for more successful and compliant drugs by releasing the drug over long period to the target organ and lowering treatment costs [14]. Nanocarriers' physicochemical properties allow for the efficient administration of antitubercular drugs, overcoming the limitations of conventional antitubercular therapies. NP systems are innovative and promising alternatives for increased therapeutic efficacy and reduced adverse effects of the encapsulated drugs [15, 16].

Antitubercular drug resistance or toxicity may be avoided by administering the encapsulated drugs alone or in combination to the target site [17, 18].

Although our understanding of the influence and the working of the NP on the human body has improved, but more focus and exploratory trials are needed in the formulation of diagnostic and therapeutic tools for the treatment of chronic and long-term diseases [19, 20].

3. Application of Nanomedicine

3.1 Nanomedicine and Tuberculosis Treatment:

The biggest problem associated with TB chemotherapy patient is non-compliance due to the long duration of therapy. A decrease in the frequency of dosing and duration of the treatment can beachieved by using nanomedicine approach and which can lead to a significant improvement in the TB chemotherapy.

Pandey *et al*. 2003 studied the NP formulations of front-line anti-TB drugs RF, INZ, and PZM in mice after giving of a single dose of the NP formulations, the therapeutic concentration in the cells was maintained for 9 to 11 days. Further, they also evaluated the effect of orally administered NP encapsulated drug in MT infected mice. No MT bacteria was detected on the 50th day of the study, i.e., after 5 oral doses. These results strongly indicate that NP based anti-TB therapy could be advantageous because it tends to reduces dosing frequency. Nanomedicine approach provided a significantly more residing time, and elimination half-life of the drugs when compared to orally administered formulations and resulted in an increased bioavailability for the NP- formulation (RF 12.7-fold, PZM 14.7-fold, and INZ 32.8-fold) [21, 22].

Pison et al 2006, in his study found that nebulization of the nano-encapsulated drug leads to an absence of MT bacteria after 5 doeses in the lungs of the infected animals. However, in case of conventional formulation, 46 daily doses were requiring to get similar therapeutic effect. These studies inferred that an anti-TB drug encoated with NP in the aerosol enhances the therapeutic outcome of pulmonary tuberculosis [23].

Monowar et al 2020 studied the polymeric NP formulation of EB a first line Antitubercular drug. The polymer nanoparticles of EB were able to exhibit sustained release of drug for period of 24 hrs. Hence reducing dose frequency and increasing patient compliance, which is major challenge with conventional therapy [24].

Sarvamangala et al, 2015 developed INZ nano-conjugates for increasing therapeutic efficacy. In the study, it was found that developed nano-conjugates were showed 84.3 % zone of inhibition of MT bacteria. Hence, it can be inferred that nano-conjugates could increase the efficiency of TB treatment and reduce the time of medication [25, 26].

3.2 Nanomedicine and Diagnosis of Tuberculosis

Nano-diagnostics objective is to detect the disease at the earliest possible time. To fulfill this aim, NM research and development process must identify "smart" probes that can detect diseases at single cell level. India, which has the highest TB cases in world, is conducting research into the role that NT can play in addressing such issues [27, 28].

Recently the Indian Central Scientific Instruments Organization (ICSIO) has developed a diagnostic kit based on NT, which does not necessitate the use of qualified personnel and provides portability, performance, and ease of availability [29]. The Medical Sciences Division of the U.S. Department of Energy is also working on an optical biosensor for fast TB diagnosis. A Novel NP based TB diagnosis is being developed by another group at RMIT University, in Australia [30]. This technique was based on colorimetry method.

In general, NT can have a major effect on disease detection and drug discovery methodologies. Nanodiagnostics would have an effect on the scale and pace of pharmaceutical developments in the future.. Diagnostic concepts and advancements based on NT with a molecular imaging perspective will be successful in the future [31].

3.3 Nanomedicine and Tuberculosis Vaccine

Vaccines targeting both pulmonary and systemic diseases are currently being developed. Most of them are injectable vaccines and needs to be stored at cold temperatures, needs a sterile environment and trained staff to administer. RSV (respiratory syncytial virus) vaccine is an injectable vaccine used to prevent chronic lung infections and asthma [32]. The RSV vaccine is currently unavailable due to the withdrawal of the previous one because of immunopotentiation caused by the alum adjuvant. However, a recently published study, which compared the effect of nanoemulsion adjuvant, deactivated RSV vaccine alongside an alum-adjuvant RSV vaccine. They found that the intra-nasal delivery of a nanomodified vaccine successfully immunises against RSV infection while avoiding the immunopotentiation reaction seen with alum-based vaccines [32]. In the case of tuberculosis, the BCG vaccine is only safe for the first ten years, and its effectiveness in adulthood is significatly variable, and potentially leading to the development of DR bacteria strains. Formulation of nanomodified vaccine will improve the efficacy of currently available vaccines. The nanomodified BCG vaccine for tuberculosis has shown promise and has the potential to overcome the limitations of traditional BCG efficacy. To establish this approach, Ballester *et al*., (2011), Researchers attempted to conjugate the TB antigen (Ag85B) with 30 nm polypropylene NP and compare its effectiveness to the antigen alone on pulmonary and intra-dermal routes using a murine model of TB. They found that conjugating the vaccine greatly improved its efficacy against the antigen alone. They also showed that pulmonary delivery is more effective than intra-dermal delivery in providing tuberculosis immunity [33].

3.4 Nanomedicine and Drug Resistance Tuberculosis

Drug resistance TB is a serious issue worldwide in advancement made in TB treatment and control. The pathogen that causes drug resistance develops it because of the improper use of drugs in the care of drug-susceptible TB patients. This inappropriate use may be because of the application of incorrect treatment regime and patient non-compliance with the treatment course. MDR-TB cases accounted for 5% of all TB cases worldwide in 2013, with 3.5 percent being newly diagnosed cases and 20.5 percent being previously treated cases [33]. The demerit of traditional TB drug formulation is their ineffectiveness to kill intracellular pathogens due to their poor bioavailability and penetration capacity in the target pathogens. NP have the ability to adsorb to the surface of bacteria, and the encapsulated drug within NP acts as a depot for the drug, increasing its bioavailability and solving dug resistance problem [34, 35].

Lectin-decorated nanoparticles have been used to target the microorganism surface receptors to enhance the therapeutic effectiveness of drug. When given intra-nasally, RIF-Loaded PLGA microspheres caused less toxicity than the free drug and effectively decreased the pulmonary burden of MT [36].

Artemisinin drugs, nano-chitosan artemisinin, as well as anti-TB drugs, were found to destroy or inhibit DR tubercle bacilli. The pharmaceutical composition had a significant curative effect on DR tuberculosis [37].

3.5 Nanomedicine and Site-Specific Tuberculosis Treatment

NT provides therapeutic agents with the benefits of controlled release and selective drug delivery, resulting in enhanced pharmacokinetics, pharmacodynamics, toxicity, immunogenicity, and efficacy. Controlled release formulations for drug delivery applications have increased significantly in recent years. These formulations use polymers with specific physical and chemical properties, such as biodegradability, biocompatibility, and pH or temperature sensitivity for various functions. For better therapeutic efficacy, the route of administration plays an essential role as the drug itself [38].

Vadkkan *et al*. 2013, synthesized stearic acid-grafted branched polyethyleneimine. They found that the long alkyl moiety of stearic acid played a key role in the micelles' ability to self-assemble. They discovered that particle size and surface charge play a role in cytotoxicity.. Nano micelles' cationic property was discovered to affect absorption into the cell. The drug-loaded nano micelles that have been spray-dried are also a good excipient for supplying xenobiotics to the lungs by dry powder inhalation technology [39].

Shah et al. 2017, fabricated 1st-generation RIF naonemulsion formulation and its successive functionalization with chitosan and chitosan-folate. The nanoemulsion formulation had more than 75% inhalational quality, as well as high lung content, increased cell internalization, and a better cytotoxic profile [40].

Liu et al. 2019 developed thermo responsive liposomes for delivery of INH to the target site for bone TB in a hydrogel system. Local drug delivery systems have a huge benefit because they deliver maximum drug to the target area with minimal systemic disclosure. The in vivo experiments revealed that the medication was readily available in the synovial fluid after injection. In addition, a cytotoxicity analysis using the MTT assay revealed no toxicity, indicating that the formulation can be used to treat bone TB [41].
Hamed et al 2019, developed a spray-dried nano-liposomes incorporated inside microparticles of moxifloxacin for better lung delivery of the drug. 4-aminophenylalphaD– manno-pyranoside was used to modify the surface, allowing for better drug absorption by lungs alveolar. The formulation revealed a biphasic release mechanism, as well as improved minimum inhibitory concentration values[42].
4. Major Hurdle with NM based Technology: There are number of obstacles that are associated with NM technologies [43].

- Development of NM based technology requires lots of cost.
- Human trials are required for NM based technology to evaluate effectiveness.
- The parenteral administration needs supervision and trained person.
- NM based formulation require specialized storage condition which is mostly unfeasible in low-income group area.

5. Conclusion:

The development of NP technology for TB treatment is a cost effective and encouraging tool. The drawbacks of traditional therapy can be easily overcome using NP technology.

In addition, extensive research on NP technology could aid in the delivery of antimicrobial drugs to target sites and the treatment of serious diseases. Their benefits, such as improved bioavailability and reduced dosing frequency, continue to be a solid foundation for better disease control. All of these factors are important in lowering the cost of TB care and improving TB control. The choice of, Scale –up, processing polymer carrier, stability, and toxicity of the nano-formulation, on the other hand, are important concerns. However due to the difficulties of discovering novel anti-TB drugs, NM has arisen as a viable platform for TB treatment.

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