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### RESEARCH ARTICLE

## NANOPARTICLES: NEOTERIC PLATFORM AGAINST MULTI DRUG RESISTANCE TUBERCULOSIS

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#### Abstract

Tuberculosis caused by Mycobacterium strains intracellular bacilli is a pernicious infection posing global menace to public health. It kills about 2 million people per year worldwide and has been declared as "Global emergency" by WHO. Nano particulate drug delivery systems are suitable for targeting chronic intracellular infections such as tuberculosis. Given the options for oral as well as parenteral therapy the very nature of the disease and its complex treatment urges one to emphasize on the oral route for controlled drug delivery. Treatment of drug susceptible TB continues for a period of 6 – 9 months, while Multi Drug Resistance TB requires rigorous treatment with second line anti-TB drugs that has many unacceptable systemic side effects. These arduous treatment regimens and lack of knowledge regarding the importance of completing the treatment course can cause non-adherence of patient to the medications that remains the most important reason for treatment failure. Targeted drug delivery in the form of nanoparticles holds significance in combating TB bacilli by prolonged and intracellular drug release. Pending are the discovery of more potent anti-tuberculosis drugs, nanotechnology based intermittent chemotherapy provides a novel and sound platform for an onslaught against tuberculosis. The current review discusses the traditional anti-TB drugs and the advantages of targeted delivery of nanoparticles over conventional treatment in terms of efficacy, reduced frequency of dosing, decreased duration of treatment regimens and reduced systemic toxicity.

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#### Introduction:-

"Tuberculosis, commonly known as TB, is a contagious and an often severe airborne disease caused by a bacterial infection. TB typically affects the lungs, but it also may affect any other organ of the body."<sup>[1]</sup> In spite of tremendous efforts to surmount the TB epidemic across the world, it remains to be one of the most horrendous threats for the global health communities. As per Global TB control report of 2012, Mycobacterium, causing infection is the culprit for 1.3 million people's death and 8.6 million new active infections. It has been estimated that 64% of TB incidents were reported to National TB Programs in 2013.<sup>[2]</sup> According to reports of WHO, TB is one of the three major

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causes of deaths among females of age group 15 - 44 years and approximately 320000 women died due to TB in 2010. <sup>[3]</sup> Of 34,000 MDR patients enrolled on treatment in 2010, only 48% successfully completed treatment and 15% died. Among 795 XDR cases, mortality rate was approximately 50%. Only about 50% of detected cases in cohort study conducted in 2012 were successfully treated. <sup>[4]</sup>

Although the treatment of TB has been around for approximately 50 years but it remains to be the leading bacterial infection caused by Mycobacterium, which can produce either a silent, latent or active disease. A person's lifetime risk of active TB is 10% once infected by Mycobacterium bacilli, it becomes 4-16 times for patients with underlying immunosuppression (e.g.- Renal failure, cancer etc.) and it dreadfully becomes 100 times for HIV infected patients <sup>[5,6]</sup>

Treatment of drug susceptible, uncomplicated Tb typically requires minimum of 6 months. One of the major problems with such arduous and demanding regimen is poor medication compliance that can eventually lead to MDR-TB. Exhaustive undertakings have helped to resolve stumbling blocks of medication compliance, toxicity and frequency of dosing by targeting the site of infection via carrier based drug delivery system that can be important therapeutic approach for better health outcomes. In the era of nanotechnology, its most promising application is targeted drug delivery and nanoparticles forms kernel of nanomedicine. Owing to its nanoscale size and large surface to volume ratio, nanoparticles readily interact with biomolecules at cellular level, thus it can be potential diagnostic and therapeutic tool. Nanoparticles have been scrutinized for drug solubility, stabilization and targeted delivery. In uncomplicated TB, targeting lymph nodes has proved to be a propitious strategy. Nevertheless, so far diminutive evidence is available for determining its influence in drug-resistant TB. Even though developing new anti-TB drugs is of prime importance in an onslaught against intracellular bacilli, formulating anti-TB drugs in nanoparticle based drug delivery system appears to be a viable and effective alternative which not only reduces the duration of regimen, dosing frequency, systemic toxicity and drug interactions but also delivers the drug efficaciously and acts as silver lining in overcoming the blockades of the conventional orally administered drug regimens. Thus, eventually helps to improve patient compliance and completion rates, which has significant impact in preventing MDR-TB.

### **Background:-**

Nanoparticles as carriers of therapeutic agents in molecular targeted therapy and better diagnostic imaging are emerging as neoteric and promising platform in nanomedicine as novel therapeutics. <sup>[7]</sup> The primary intent of nanoparticles is to control and manipulate bio macromolecular constructs and supramolecular assemblies that plays a vital role to in improving the quality of human health. The advent of Nano therapeutics/ diagnostics will allow a profound understanding of both the diseases that have been a threat for human lives since ancient times and treatment to improve the human quality of life. Nanoparticles for the purpose of drug delivery can be defined as solid, submicron, colloidal particles that are of size 10-1000nm. <sup>[8]</sup> Because the diameter of smallest vessels in the human body is approx. 4micromts, the colloidal particles of >200nm are not pursued in nanomedicine. Based on their designing they are of two types:

- a) **Nanospheres:** (Matrix systems) monolithic nanoparticles in which drug is physically and uniformly dispersed throughout the polymeric matrix.
- b) **Nanocapsules:** (Vesicular systems) Nanoparticles in which the drug is concentrated in the core (hydrophilic/ hydrophobic) surrounded by a shell like wall or "capsule". <sup>[9]</sup>

### **Polymeric nanoparticles:**

Since the polymeric nanoparticles are more stable and have ease of surface modification, they are more heavily used in Nano therapeutics. <sup>[10]</sup> Nanoparticles have been made by a wide range of biocompatible and biodegradable Nano particulate substances for the sake of delivery of therapeutic compounds to their site of action. They can be made from both natural (e.g., gelatin, albumin) and synthetic (e.g., polylactides, polyalkylcyanoacrylates). <sup>[11]</sup> The era 1960's and early 1970's has witnessed the birth of polymer microparticles by the use of acrylamide polymerization technique and since then different preformed polymers have been developed by using variety of polymerization methods. The most commonly used polymers now-a-days are listed below:

**Table 1: CARRIERS USED IN DRUG DELIVERY:**<sup>[12]</sup>

<b>NATURAL CARRIERS</b>	<b>SYNTHETIC CARRIERS</b>
<b>Proteins and polypeptides</b>	<b>Aliphatic polyesters and Hydroxy acids</b>
<ul style="list-style-type: none"> <li>a. Albumin</li> <li>b. Fibrinogen/ fibrin</li> <li>c. Collagen</li> <li>d. Gelatin</li> <li>e. Casein</li> </ul>	<ul style="list-style-type: none"> <li>a. Polylactic acid</li> <li>b. Polyglycolic acid</li> <li>c. Poly (lactide-co-glycolide)</li> <li>d. Polyhydroxy butyric acid</li> <li>e. Polycaprolactone</li> </ul>
<b>Polysaccharides</b>	<b>Polyanhydrides</b>
<ul style="list-style-type: none"> <li>a. Alginic acid</li> <li>b. Starch</li> <li>c. Dextran/ Dextrin</li> <li>d. Hyaluronic acid</li> <li>e. Chitin</li> <li>f. Chitosan</li> </ul>	Poly ortho esters
	Poly alkyl cyanoacrylate
	Polyamino acids
	Polyacrylamides
	Poly alkyl carbonates

**Drug release from nanoparticles:-**

Nanoparticles are surrounded by polymers through which the drug is released by either controlled diffusion or erosion from the core across the polymeric matrix. Although the rate of drug release is dependent upon the ability of the drug to dissolve and diffuse in the polymeric matrix but it is also affected by the ionic interactions between the drug and the auxiliary ingredients added, that results in the formation of a complex which is less water soluble that could cause slow drug release.<sup>[13]</sup>

**Drawbacks of conventional atd therapy:-**

Conventional ATD therapy is very effective; however, it does have its own downsides. Majority of TB cases reported are of pulmonary TB (more than 80%) that demands administration of high doses since only small fraction of the total dose given via oral route reaches the macrophages in the lungs. And this small fraction is cleared from the lungs within a short span of time thus requiring the administration of multiple ATDs regularly, a regimen to which not all the patients show good compliance. On top of that, the continuous increase in MDR TB incidences has to be addressed properly since the commonly used second line ATD are not only more costly and toxic but also has longer duration of regimens that contributes to patient non-compliance which is the cardinal reason for the development of MDR-TB.<sup>[14]</sup>

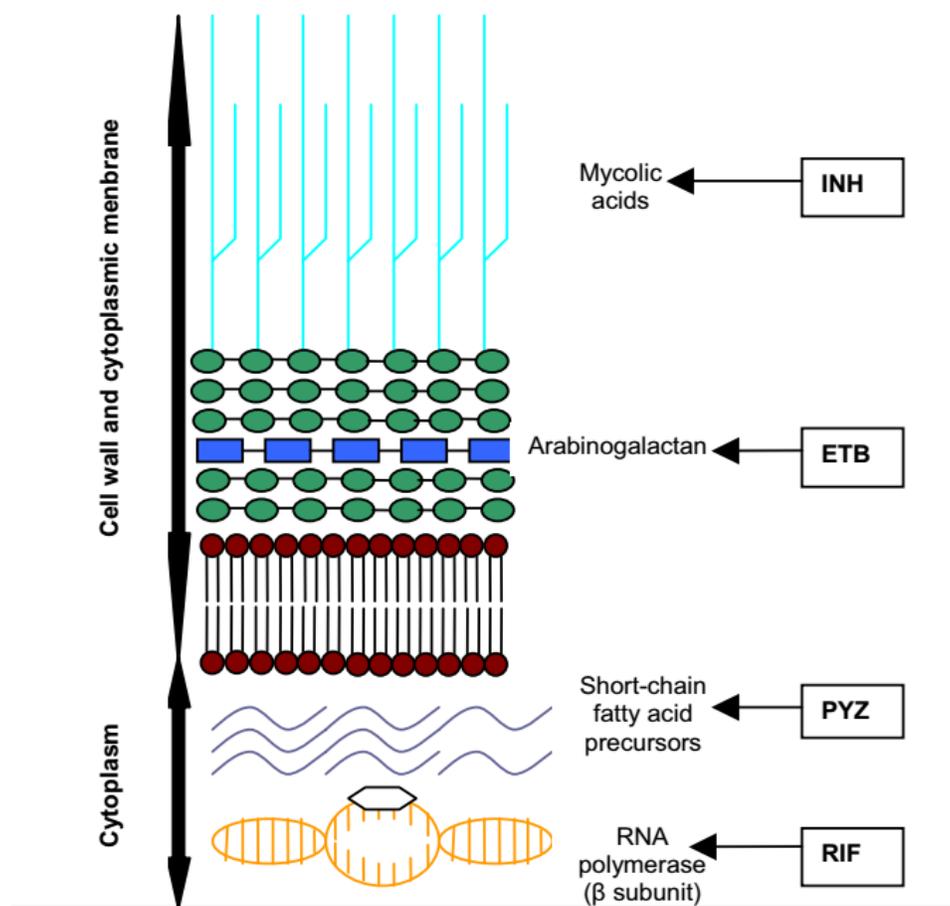


Figure1: Site of action of first line ATDs:<sup>[15]</sup>

Table2: First line agents of tuberculosis:<sup>[16,17]</sup>

DRUGS	MECHANISM OF ACTION	ACTS AGAINST
Isoniazid	Inhibiting the cell wall synthesis	Rapidly multiplying bacteria
Pyrazinamide	Inhibiting and depleting the membrane energy	Bacteria which can survive under acidic pH and has lower metabolic activity
Ethambutol	Inhibiting the cell wall synthesis	Rapidly multiplying bacteria and used against INH resistant strains
Rifampicin	Inhibiting the nucleic acid synthesis	Bacteria with spurts of metabolism, dormant stage followed by short and active span growth and metabolism

#### 4. Advantages of nanoparticle drug delivery over conventional atd therapy:

However, nanoparticle based drug delivery can be tailored to achieve sustained, controlled and targeted drug delivery, improve bioavailability, increased solubilization of drug.

It has been established by various studies that nanoparticle based drug delivery system has many advantages over the conventional therapy. Some of them are enumerated below:

1. The particle size and surface properties can be altered easily in order to target the drug by both mechanisms i.e., active and passive delivery
2. Controlled release and particle degradation can be readily manipulated by using appropriate matrix polymer
3. It can be administered by various routes such as oral, pulmonary, subcutaneous etc.

4. Improved bioavailability by enhancing water solubility
5. Increases the elimination half life of the drug
6. Targets the drug to specific locations in the body by binding the drug with specific ligands or by magnetic guidance.

This leads to reduction of dose and systemic toxicity, thus enabling the safe delivery of therapeutic agents to the target organ. <sup>[18]</sup>

**Table 3:** Properties of Anti TB drugs that can be improved with the use of proper drug delivery system:<sup>[12]</sup>

Anti- Tuberculosis Drugs	Properties
Rifampicin	Food interactions Drug-drug interactions
Ethambutol	Low shelf life
Streptomycin	Poor intestinal absorption
Metronidazole	Unpalatability
Danazol	Poor solubility in intestinal fluid
Azathioprine	Short duration of stay
Clotrimoxazole	Sub therapeutic levels in plasma

### Nanoparticles characteristics to be considered when used for drug delivery:

#### 1. Particle size:

With the particle size, one can determine the biological fate and the accuracy of target delivery of the system. It also influences other vital properties such as rate of drug release, stability, dose to be incorporated etc.

The size of the nanoparticles can be determined by two primary methods;

- a) Photon correlation spectroscopy
- b) Dynamic light scattering

Transmission electron spectroscopy (TES) and scanning electron spectroscopy (SEM) are then used to verify the results obtained. <sup>[18]</sup>

#### 2. Surface properties:

Once nanoparticles (surface non-modified/conventional) are in the blood stream, they are rapidly cleared and opsonized by the MPS (mononuclear phagocyte system). <sup>[19]</sup> Therefore, there is demanding need of coating the non-modified nanoparticles with polymer/ surfactants or formulating with the biodegradable polymers with hydrophilic properties.

Example: Polyethylene glycol (PEG), polyethylene oxide, polyoxamer, poloxamine and polysorbate 80 (Tween 80). <sup>[20]</sup>

It is important to determine the surface charge properties of the nanoparticles. The most common method is by using zeta potential. <sup>[21]</sup> The surface charge is greatly influenced by the medium of dispersion and composition of the particles. <sup>[22]</sup>

#### 3. Drug entrapment:

Drug loading/ entrapment primarily depends upon drug solubility with both the matrix and the excipients. <sup>[23]</sup> The macromolecules or proteins loaded within the nanoparticles has more loading efficacy when loaded at or near their isoelectric point (IP). <sup>[24]</sup> Studies have shown that in smaller molecules, the ionic interaction between the drug and the matrix can increase the drug loading. <sup>[13]</sup>

#### 4. Drug release:

In polymer coated nanoparticles, diffusion of the drug across the membrane is the rate limiting step. Ionic interactions influence the rate of drug release. Example; A poorly water soluble compound can be formed due to the

interaction between the drug and the excipient which will slow the rate of drug release. The rate of drug release can be increased by decreasing the interactions between drug and the matrix by adding the excipients like ethylene oxide-propylene oxide block copolymer (PEO-PPO) to chitosan.<sup>[25]</sup>

### 5. Target delivery:

This can be two types:

- ✓ Active delivery
- ✓ Passive delivery

**Active delivery** involves the release of encapsulated drug in the nanoparticle which is bonded to the carrier only when it comes in contact with the specific ligand or the tissue. Whereas in **passive delivery**, the drug encapsulated in the nanoparticles are passively released after it has reached the targeted organ.<sup>[26]</sup>

#### Different delivery systems of ATDs:

1. Orally administered NP
  - ✓ Non-surface Functionalized
  - ✓ Surface Functionalized
- a. Inhalational NP
- b. Injectables NP
  - Intravenous
  - Subcutaneous
  - Intramuscular

#### a. Orally administered nanoparticles:

##### 1. Non-surface functionalized nanoparticles:

Panday et al. designed two therapeutic regimens and sub categorized each regimen into free drug or PLG based drugs.

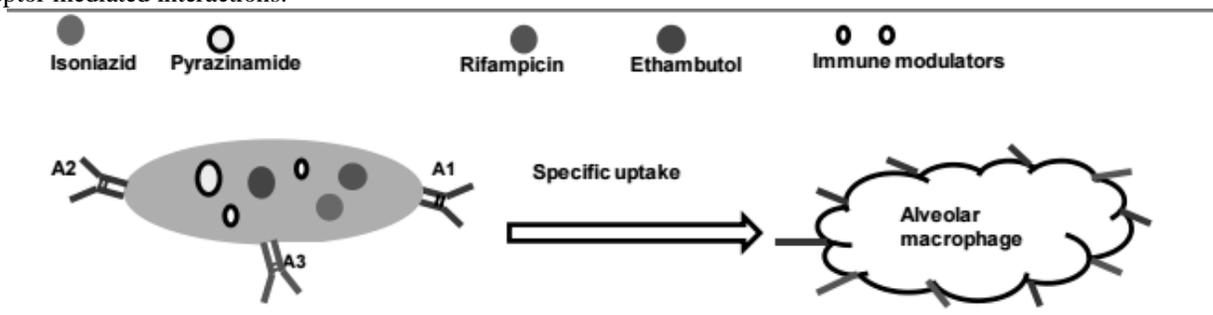
The three first line Anti-TB drugs INH, RIF and PZA were encapsulated in PLG based NP (prepared by solvent evaporation and double emulsion technique). This experiment concluded promising results after only one therapeutic dose of ATD-loaded PLG nanoparticles was administered. The MIC of ethambutol, rifampicin, isoniazid / pyrazinamide was found in the blood even after 3,6 and 8 days respectively which is a remarkable discovery since free drug concentrations were undetectable only after 12 h of oral administration. The first line drugs of TB i.e., Isoniazid, Rifampicin and Pyrazinamide when encapsulated with PLG nanoparticles and administered via oral route in mice have shown propitious results. The drugs were detected in the blood circulation even after 4 days (for RIM) and 9 days (for INZ and PYZ) and duration of drug stay in tissues was about 9-10 days, while, for free drugs duration of drug stay was up to 24 hours. ATD-loaded nanoparticles have efficacy equal to 46 conventional doses when administered IV or IM in mice and guinea pigs respectively. When the ATD nanoparticles were given (5 oral doses every 10<sup>th</sup> day), it resulted in complete sterilization of infection. The study has not shown any hepatotoxicity. With 10 X and 150 X therapeutic doses, the time of drug stay for free drugs in the tissues was 24 h, while, it was 9-10 days for PLG encapsulated drugs. However, 150 X therapeutic dose of free drugs was found to be lethal.<sup>[27]</sup>

In another study, o-stearyl amylopectin was tagged to liposomal encapsulated INH and RIF and administered intravenously in Mtb infected mice. The tagging with o-stearyl amylopectin facilitates targeting the bronchial tissue. The bacterial load was cleared within 6 weeks when it was given once a week by using a quarter of their total therapeutic dose. This study also has shown no sign of hepatotoxicity.<sup>[28]</sup>

##### 2. Surface Functionalized Nanoparticles:

The bioadhesive properties of the PLG - NP greatly influence bioavailability of the encapsulated drug. The bioadhesive drug delivery system helps to improve/ enhance the bioavailability of the administered drug by increasing its residence time in the GIT, which in turn increases its contact time with gastric mucosal epithelium. Bioadhesion of drug carriers to the mucosal surface in the GIT is limited by the turnover time of the mucosal layer, which is approximately few hours for almost all of the mucosal surfaces. Polymeric carriers conjugated with specific

cytoadhesive ligands that can undergo reversible and non-covalent binding with the gastric epithelial surface by receptor mediated interactions.<sup>[29]</sup>



**Figure 2:-** Surface functionalized encapsulated nanoparticles for the specific surface markers on the alveolar macrophages<sup>[30]</sup>

The role of Lectins as mucoadhesives has been exploited because of their biorecognition interactions with the glycosylated structures and their ability of resistant to proteolytic degradation. Lectins mediate:<sup>[31]</sup>

- ✓ Mucoadhesion
- ✓ Cytoadhesion
- ✓ Cytoinvasion of drugs

Lectins are structurally diverse group of proteins, which can be found in varied organisms such as viruses, plants and humans. Wheat germ agglutinin (WGA) has been preferably used in the drug delivery because of it is one of the least immunogenic lectins and also its receptor can be found on both gastric and alveolar epithelia. WGA functionalized poly (lactide-co-glycolide) nanoparticles based formulations of ATD of size 350- 400 nm showed dramatic improvement in the sustained released property. INZ and RIF was present in the plasma for 13 days and PYZ for 7 days and were detectable in tissues for up to 15 days well above their MIC. Three doses given for 15 days were as efficient as 45 doses of free drugs administered orally and Mycobacterium cfu was almost cleared following administration of 5 doses every 10th day. This study has reported that WGA functionalized PLG NP loaded with ATD results in enhanced bioavailability, decreased dosing frequency and duration of regimen which ultimately affects patient compliance because of cost effectiveness for a full course (1\$ vs 17\$ mg/kg) in guinea pigs.<sup>[29]</sup>

**b. INHALATIONAL NANOPARTICLES (Pulmonary route):-**Pulmonary route is the novel approach in delivering the ATDs directly and thus provides a more efficient platform in combating pulmonary TB.

**Potential advantages of pulmonary route:**<sup>[32,33]</sup>

- Administration of drug directly to the bronchial tissue.
- Less dose is required.
- Reduced dosing frequency
- Since the rest of the body is not exposed to the action of drug administered, the incidences of systemic side effects decreases.
- Onset of action is fast.
- Bioavailability is relatively high.
- Better mucosal adherence.
- Bypasses first pass metabolism.

**Disadvantages of Pulmonary route:**<sup>[32,33]</sup>

- Administration of drug requires specific device
- Supervision is required
- Administration of drug involves technique.

Because alveolar macrophages are known to be the pivotal abode of Mycobacterium tuberculosis, there have been renewed interests in targeting these cells. Phagocytic cells have relatively selective ability for cellular uptake of NP

which makes them easier targets for nanoparticle encapsulated ATDs. INH, RIF and PYZ were formulated in PLG based co-encapsulated nanoparticles and were administered to experimentally infected guinea pigs animal models via aerosol route. The mass median aerodynamic diameter was about 1.88 micrometers which is favorable for deep bronchial delivery. A single nebulization was enough to maintain therapeutic concentrations in plasma for approx. 6-9 days and in lungs for 9-11 days. There was drastic improvement in other properties as, such as, plasma elimination half-life, mean residence time and absolute bioavailability compared with the unconjugated or unbound drug. Further, 5 nebulized doses given on every 10<sup>th</sup> day resulted in undetected cfu which is equiefficient to 46 conventional oral doses.<sup>[34]</sup> This study has broadened the horizon for co-administering multiple ATD that has helped to substantially improve the therapeutic response.

- ✦ **Sung JC et al.**, formulated RIF for aerosol delivery in a dry powder 'porous nanoparticle-aggregate particle'(PNAP) form by solvent evaporation process and spray dried in PNAP, which has shelf stability, effective dispersibility and extended release in lungs and systemic drug delivery. The spray dried RIF administered to guinea pigs by intrathecal insufflation revealed that pulmonary drug levels was maintained for 8 hours and systemic drug levels were obtained within 6-8 hours.<sup>[35]</sup>
- ✦ In another study, RIF poly (lactic-co-glycolic acid) PLGA nanoparticles (RIF/PLGA nanoparticles) were formulated in mannitol microspheres. It was then administered in rats using four-fluid nozzle spray dryer in one step. In vivo studies have concluded that RIF's uptake for RIF/PLGA/MAN microspheres was higher, approx. 4% at 1 hr. of administration that has further increased to 9.3% at 4 hour; in contrast to uptake of RIF from RIF/PLGA microspheres which was relatively smaller.<sup>[36]</sup>
- ✦ Lectin receptors are quiet extensively distributed in the respiratory tract so the chemotherapeutic potential of lectin functionalized PLG-NP was assessed as well. Nebulization of Lectin functionalized PLG-NP to guinea pigs, resulted in maintenance of therapeutic drug concentrations in plasma for 6-10 days and in organs for 15 days. Various experimental studies has shown that 46 conventional doses can be reduced to 5 nebulized doses of PLG – NP, that can be further reduced to only 3 lectin based PLGNP<sup>[37]</sup>

### C. Injectable nanoparticles:

Different routes by which ATD – NP can be injected includes:

1. Intravenous
2. Subcutaneous
3. Intramuscular

Compared to conventionally administered ATD of 35 oral doses, when the infected mice were given only a single injection of drug loaded PLG-NP via subcutaneous route, it showed not only remarkable sustained drug levels in the plasma for about 32 days and in the organs (lungs/spleen) for about 36 days but also better efficacy by completing eliminating the Mycobacterial bacilli from the organs. At the site of injection, the nanoparticles form drug depot from which the drug is slowly released into the blood circulation.<sup>[38]</sup> Poly (butyl cyanoacrylate) nanoparticles loaded with INH and streptomycin showed elevated accumulation levels in the cultivated human blood monocytes. Thus, resulted in enhanced activity against intracellular M. tuberculosis bacilli. Similar results were shown by the encapsulated ciprofloxacin and RMP in the infected macrophages. However, previous in vitro studies has concluded that increased intracellular drug accumulation levels rarely, simultaneously increases the activity of the drugs against intracellular bacteria compared to the extracellular bacterial population.<sup>[39]</sup>

**Table 4:-** Techniques involved in preparation of PLGbased nanoparticles<sup>[12]</sup>

TECHNIQUES INVOLVED	MERITS/DEMERITS
Emulsion / evaporation	Poor entrapment of hydrophilic drugs
Double Emulsion / evaporation	Good entrapment of both hydrophilic and hydrophobic drugs
Salting out	Long purification method
Emulsification diffusion	Rapid technique
Solvent displacement / non precipitation	Hydrophilic drugs has poor entrapment
Emulsification-diffusion-evaporation	Size and shape of the nanoparticles are better controlled

**TOXICITY EVALUATION OF PLG NANOPARTICLES BASED ATDs:**

The toxicity studies include single dose toxicity (or acute toxicity that determines median lethal dose LD50 I.e., the single dose produces 50% mortality of animals within 14 days), and multiple dose toxicity which further includes sub-acute toxicity for 28 days and chronic toxicity for 90 days.

**Panday et al.**, reported detailed toxicological and chemotherapeutic evaluation of INH, RIF, PYZ and EMB loaded PLG- NP. The single dose administration of PLG based nanoparticles not only didn't show any sign of adverse effects but also when they were administered several times higher than the recommended therapeutic dose, showed similar results. On the other hand, conventional free drugs were lethal when given at equivalent higher doses. The acute and chronic toxicity studies conducted based on survival, gross pathology, histopathology, blood biochemistry and hematology observed no evidence of toxicity for the PLG-NP based ATDs.<sup>[40]</sup> The remarkably positive safety profile put forth by the above study provides a solid foundation for the researchers to scrutinize it further for oral administration and in higher animal models like guinea pigs.

**Mdr tuberculosis and nanoparticle technology:**

The above studies are done in relation to the drug susceptible TB, however they are significantly relevant in paving the way for surmounting not only the drug susceptible TB but also the horrendous MDR-TB. The outstanding results of nanoparticles based ATD of improved bioavailability, sustained and targeted (intracellular) drug delivery and improved pharmacokinetic profiles has provided renewed approach against Mycobacterium bacilli as it directly affects the treatment duration, frequency of administration and pill burden. Since the researchers around the world have failed to categorize or put forth any anti-tuberculosis drug as the first line agent against MDR-TB, the most immediate and reliable approach is to treat the drug susceptible TB efficiently. However, the patient compliance and proper infection control are the two cardinal factors that effects the treatment of drug susceptible TB which can be improved by reducing the duration of regimen, frequency, pill burden, increased bioavailability, sustained therapeutic concentrations in the targeted tissues. Nanoparticles, being a cost effective alternative for lengthy and arduous regimens has potential to play significant role especially in the underdeveloped and developing countries and for the people below the poverty line who are more prone for the infection owing to their poor hygienic environments. According to WHO reports, these countries carry the burden with rates of 20 times higher than that of developed countries. The load of developing MDR TB can also be attributed to the lack of required diagnostic tools, proper health care and health care professionals. Above all, it is the financial condition of patients that is prime culprit that limits even the necessary education and transportation. These situations are ideal for the MDR TB to thrive and for the nanoparticles to unleash its possibilities. As there are no front line agents for MDR TB or XDR TB, nanotechnology can be applied to many second line agents as well. For MDR TB, the resistance profiles can vary. Recent studies have provided evidence that high dosage levels of first line ATDs, like high doses of INH can overcome the MDR TB. One of the hurdles that prevents its clinical practice is that it is irrational to believe that the regimen for which the patient developed DR TB will be successful and will have compliance for the increased regimen of the same. This is where the nanoparticle fits into the baffling puzzle against the DR TB, since, nanoparticle drug delivery of INH reduces the regimen while simultaneously increasing the therapeutic dosage levels. In ideal conditions it is unacceptable to increase the dose of the drugs for combating the infection, however, in resource constrained settings it is the only viable option that could be lifesaving not just for the patient but also for the community as a whole by reducing the epidemic.

**Barriers to overcome:**

Despite being a feasible alternative, there are a number of barriers that has prevented the nanoparticles based ATDs to enter into the human trials.

**Table 5:-**Barriers to overcome:

- |  |
|--|
| <ul style="list-style-type: none"> <li>• Removing the residual organic solvent</li> <li>• High quality controls to maintain batch-batch uniformity</li> <li>• Specific Storage conditions required</li> <li>• Stability studies to evaluate shelf life of formulation</li> </ul> |
|--|

Effective pulmonary administration of drugs (insufflation and nebulization). In the large scale production of ATD based NP using synthetic polymers, removing the residual organic solvents is a limitation. It can be addressed by using temperature controlled vacuum drying, which will increase the production cost. Using a natural polymer like

alginate can be an affordable alternative. As in animal models certain pivotal issues have not been solved to mimic the human diseases and drug therapies, the technology has not entered the clinical trials. To maintain the batch-batch consistency of nanoparticles loaded drug, efficient quality control measures are required. PLG should be stored at low temperatures; hence the rigorous stability studies are required to evaluate the shelf life of the formulations. It becomes an obstacle in rural areas of developing countries with poor storage conditions. The sustained delivery of different formulations in animal models is not the representative of dosing schedule in human subjects, which can be commented upon once the clinical trials in human subjects have been done.<sup>[13]</sup>

### **Future prospects:**

The emergence of the MDR TB and XDR TB has posed an urgent threat globally that needs to be addressed effectively. As the researchers around the world has failed to propose first line drugs in MDR TB, it is the call of the hour to explore alternative and feasible strategies. Although the continuous efforts to discover new anti-TB drugs and to evaluate their efficacy and safety should be the priority, however, eradicating TB requires the new drug delivery systems as well. Animal studies of nanoparticle technology has given a new ray of hope to fight this trending global health threat. Due to the obstacles mentioned above, nanoparticle based ATDs have not entered the human trials. Studies should be directed towards overcoming these barriers and evaluating the performance of this novel delivery system in human trials.

### **Conclusion:**

The limitations with the conventional oral chemotherapy such as difficulty in targeting the MDR TB and latent bacteria, toxicity of second line agents and uncertainty of bacterial resistance development has pushed the researchers to explore alternative therapeutic strategies. This is where Nanotechnology fits in the 'puzzle' of combating TB epidemic.

Nanoparticle technology has proved to be most effective to enhance the therapeutic efficacy of first line ATDs among several carriers based controlled drug delivery systems. It can be administered by oral, pulmonary, intravenous, subcutaneous and intramuscular routes. It provides sustained targeted drug delivery which has the potential to reduce the frequency of drug administration and duration of treatment. Additionally, it increases the drug bioavailability and the therapeutic efficacy can be maintained even at sub-therapeutic dose levels. These favorable features eventually facilitate to improve the completion rates as it reduces the cost burden on the patients and on health infrastructure, making the DOT therapies more affordable. With respect to MDR TB Nanoparticle based chemotherapeutic drugs having advantages of improving patient adherence, reducing pill burden, and shortening duration of regimen has the potential to increase the completion rates, thus preventing an individual to progress towards MDR TB. Thus, the tremendous potential of nanoparticle technology in eradicating TB should not be understated. The performance of these neoteric modalities in human subjects is yet to be assessed and analyzed to evaluate their effectiveness in eliminating and controlling TB.

### **Conflict of interest:**

Authors have no conflict of interest.

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