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# Current Strategies and Advances in Nano Systems a Paradigm Shift in Management of Tuberculosis:A Review

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**Abstract :** Tuberculosis(TB) is recognized as the second most dreadful disease of the pulmonary system which has a potential curative pharmacotherapy's being available from decades, the length and the treatment frequency and repeated administration of drugs affects patient's day to day life abruptly. Thus, these consequences further leading to low medication lastly results in inefficient TB therapy, moreover also raises the chances of multi-drug-resistant (MDR) strains. Nanotechnology and nanomedicines are one of the breakthroughs in recent time, and drug delivery and therapeutics are not an exception for their promising applicability. With the implementation of diverse nanocarriers, drug delivery meadow is flourishing like never before.

Site specific infections like tuberculosis can be targeted via nanoparticle based drug delivery systems. Nanotechnology provides advantages over the conventional treatment in terms of drug carrier stability, carrier capacity, allowance of incorporation of both hydrophobic and hydrophilic substances, allows administration through various routes like oral, inhalational, injectable etc. and also allows controlled or sustained drug delivery from the system. These advantages of nanotechnology further improves bioavailability, avoids patient non compliance due to reduction in the dosing frequency which can overcome the demerits of a conventional system. The present review methodically covers the recent progress and developments in diverse nanocarriers based drug delivery systems for a better therapeutic outcome and patient compliance.

**Keywords :** Anti-tubercular drugs, Drug delivery, Therapy, Tuberculosis, Nanotechnology.

## 1. Introduction

Tuberculosis(TB), a respiratory infection which is caused by a bacterium called *Mycobacteriumtuberculosis*(**Figure1**), which is infectious burden all over the world. TB, a pervasive and deadly infectious disease of the respiratory system, is one of the main challenges in public health.[1]Worldwide, approximately 2 billion people are currently infected with *Mycobacterium tuberculosis*, representing about 30% of the global population.

TB is the second most deadly infectious disease after HIV/AIDS.In their most recent report, the WHO revealed that 9.2 million peopledevelop the disease every year with an annual mortality rate of1.7 million people.TB infection is usually initiated by the entry of the mycobacteriumto the respiratory system in the form of aerosol droplets.[2] Bacteria are non-specifically phagocytosed by alveolar macrophages these alveolar

macrophages process thebacterial antigens and present them to lymphocytes T. Then, thenumber of pathogens increases exponentially by killing host cells andspreading locally to regional lymph nodes in the lungs by lymphaticcirculation (3 to 8 weeks after infection). Later on, dissemination ofthe bacilli from the infected lungs to distant highly irrigated organs(e.g. CNS, spongy bone, liver, kidneys and genitalia) takes place(3 months after infection). At this stage, acute tuberculosis meningitisor disseminated TB can sometimes result in death. The release of thebacteria to the pleura 3 to 7 months after infection results in pleurisy.Finally, extra-pulmonary manifestations (e.g. lesions in bones andjoints) can appear. Having expressed this, a small percentage ofthe new cases are extrapulmonary (e.g. CNS and lymph nodes).

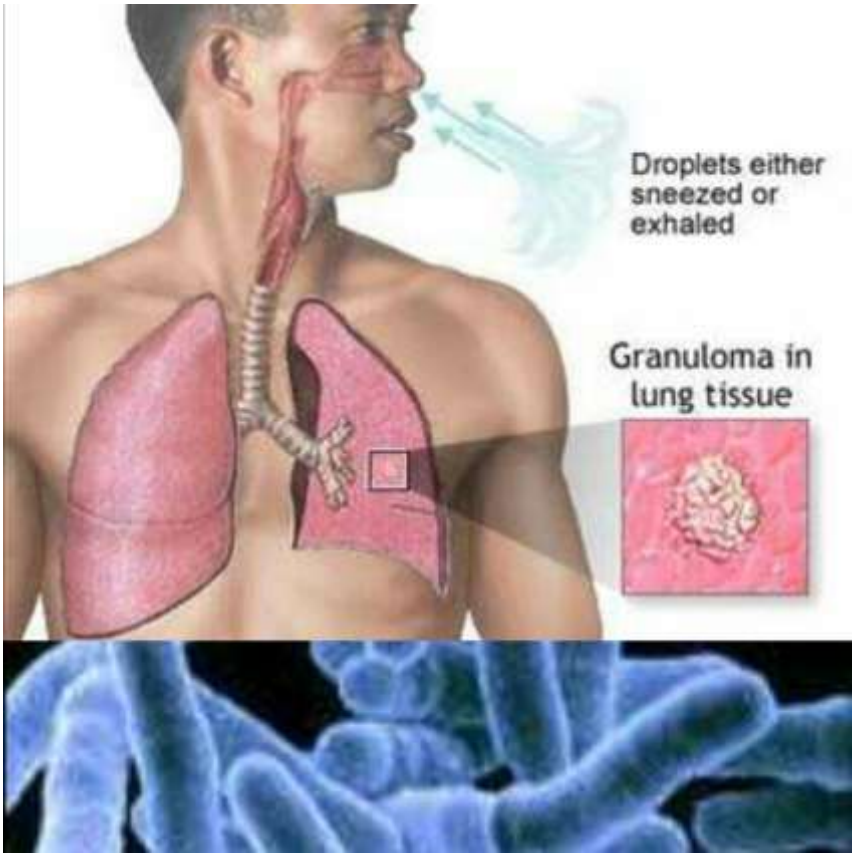


**Figure1: Structure of *Mycobacterium tuberculosis* and the lungs infected with TB.**

The emergence of multidrug-resistant strains and lack of effective anti-TB drugs are threatening the future control of TB. The present multidrug regimen against TB needs daily administration for atleast 6 months and patients often fail to follow this complex regimen for such long interval, thus leading to patient non-compliance and treatment related side effects. To avoid daily dosing, application of nanotechnology is a promising solution by a virtue of sustained drug release. Nanotechnology based rational targeting may improve therapeutic success by limiting adverse drug effects and requiring less frequent administration regimens, thus resulting in higher patient compliance, and thus attain higher adherence levels.

## 2. Nanotechnological Advances

### 2.1. Liposomes

Liposomes[3] by definition are tiny spherical bubbles composed of lipid bilayers membrane with an aqueous core (**figure 2**). These serve as common carriers for drugs such as gentamicin, sparfloxacin, amikacin, streptomycin and many others, depending on their sustainable biological compatibility. Phosphotidylcholine is the most commonly used lipid in liposomal preparation besides using cholesterol (for maintaining rigidity and stability) dicetylphosphate, o-stearoyl amylopectin, distearoylphosphatidylethanolamine and polyethylene glycol.

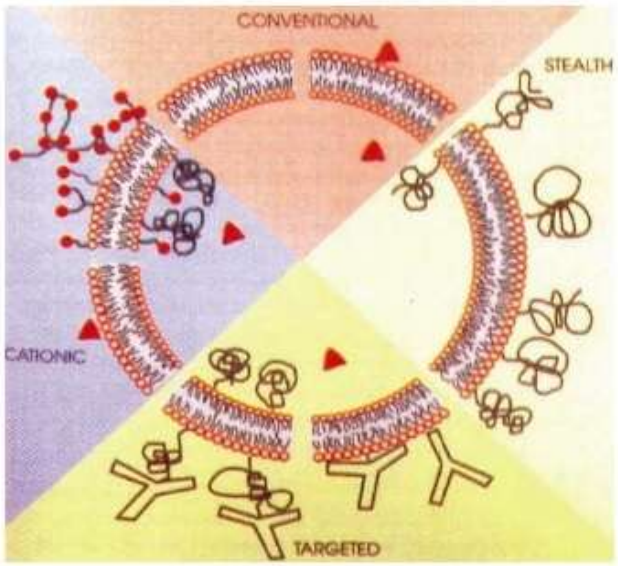


**Figure 2: Types of liposomes: conventional (CL) –phosphatidylcholine/cholesterol; cationic- addition of positivecharge to CL; stealth – coupling polyethylene glycol to CL;targeted – coupling ligands (e.g. O-SAP) to CL. In case of solidlipid nanoparticles, there is a solid core instead of the aqueouscavity of liposomes.**

Liposomes with PEG considerably enhances theircirculatory lifespan in the blood stream [4].Another group of researchers have studied liposomal-mediated rifabutin delivery in spleen, liver andlungs of mice infected with TB and the study showeda significant decrease in bacterial load when compared with drug delivery without liposomal carriers[5]. Drug delivery via liposomes is summarized in **Table 1**given below.

**Table 1:liposomes based drug delivery approaches for TB.**

| Drug | Formulation | *Mycobacterium species* | Effects | Animal model | References |
|---|---|---|---|---|---|
| gentamicin | Lipid(95% pure ePC), methylene chloride solution, gentamicin sulfate and normal saline solution | *Mycobacterium avium* complex | Reduced viable cell counts in spleen and liver | Beige mouse | 6 |
| sparfloxacin | Chloroform solutions of PG, PC, CH and sparfloxacin at a 1:1:1:0.4 molar ratio | *Mycobacterium avium* complex | Significant reduced growth rate | Beige mouse | 7 |
| amikacin | Modified ethanol injection method | *Mycobacterium avium* complex | Reduced bacterial replication, high and sustained drug level in infected tissues | Murine mouse | 8 |
| streptmycin | Multilamellar liposomes | *Mycobacterium avium* | Increased chemotherapeutic efficacy | Beige mouse | 9 |

| | | | | | |
|---|---|---|---|---|---|
| Isoniazid rifampin | Multilamellar liposomes containimgePC CH, DCP and DSPE-PEG | *Mycobacterium tuberculosis* | Controlled drug release and site directed delivery | Mouse | 10 |
| pyrzinamide | Dipalmitoyl PC[7]:CH[2] neutral and diplamitoylPC[7]:CH[2]: DCP[1] negatively charged | *Mycobacterium tuberculosis* | High therapeutic efficacy | Mouse | 11 |
| clofazimine | DMPC-DMPG(7:3) and clofazimine(drug:lipid, 1:!5) in 80% tertiary butanol | *Mycobacterium tuberculosis* | Reduced cfuwuth no toxicity | BALB/c mouse | 12 |

cfu, colony-forming unit; CH, cholesterol; DCP, dicetylphosphate; DMPC, L-a-dimyristoylphosphatidyl choline; DMPG, L-a-dimyristoylphosphatidyl glycerol; DSPE-PEG 2000, distearoylphosphatidylethanol aminepolyethyleneglycol 2000; ePC,eggphosphatidylcholine; PC, phosphatidylcholine; PG, phosphatidylglycerol.

### 2.2. Polymeric Nanoparticles

Polymeric nanoparticles possess very good bio-compatible and biodegradable features that makethem sustainable candidates for use as drug deliverycarriers. Polymeric nanoparticles are structurallymuch more stable and can be synthesized withvarious properties (drug release profile, zeta potential) by selecting different polymer lengths, surfactants, monomer dimensions and choice of organicsolvents. Polymeric nanoparticles contain emblematic functional groups that can be transformedaccording to either structural moiety of drugs ortargeted ligands. Researchers have enhanced theefficacy of these nanoparticles by structurally modifying their surface with wheat gram agglutinin[13].Further, lectin-conjugated nanoparticles can considerably improve mucoadhesion and biorecognition of glycosylated structures that are displayedon bacterial cell wall and hence induce a prolongedserum half-life.[14] Drug delivery via polymericnanoparticles is summarized in **Table 2**.

**Table 2:anti-tubercular drug delivery via polymeric nanoparticles.**

| Drug | Formulation | *Mycobacterium species* | Effects | Animal model | Reference |
|---|---|---|---|---|---|
| Moxifloxacin | Poly(butyl cyanoacrylate) nanoparticle | *Mycobacterium tuberculosis* | High drug payload | - | 15 |
| Isoniazid | Polylactic-co-glycolic acid(PLGA) co-polymer | *Mycobacterium tuberculosis* | Drug remain for prolonged period | Rabbit | 16 |
| Rifampicin, isoniazid,pyrazinamide and ethambutol | Alginate nanoparticle | *Mycobacterium tuberculosis* | High drug payload,improved pharmacokinetic high therapeutic efficacy | Mouse | 17 |
| Rifampicin, isoniazid,pyrazinamide and ethambutol | PLG nanoparticle | *Mycobacterium tuberculosis* | Enhanced bioavailability, improved pharmacodynamics | Murine mouse | 18 |

| | | | | | |
|---|---|---|---|---|---|
| Ethionamide | PLGA nanoparticles | *Mycobacterium tuberculosis* | Improved pharmacodynamics | Mouse | 19 |
| Rifampicin | PLGA nano-particles in dried powder form porousnano-particle aggregate particle | *Mycobacterium tuberculosis* | Shelf stability, effective dispersibilityand extended release with local lung and systemic drugdelivery | Guinea pigs | 20 |

**2.3. Dendrimers:**

Dendrimers are long-chained, repeated three-dimensional arrangements of a group of atoms.These are synthetic nanomaterials which are 5-10 nm in diameter. They are very versatile moleculeswith regard to their geometry and multifunctionalnature. In a comprehensive review, Cheng *et al.*[22]have comprehensively discussed about the optimized drug delivery considerations for dendrimersynthesis and the different variations and combinations. A range of different molecules can be coupledto these three regions, which is the reason forhigh functionality of these molecules. Each of theseregions possesses different functionalities and this iswhy the properties such as solubility, thermalstability and the like can be easily manipulatedfor a range of applications[23].With dendrimers, it is possible to have arrangements carrying hydrophilic materials on the outercore and hydrophobic inside core .Thisarrangement forms the basic formulation for theuse of dendrimers in drug delivery applications.

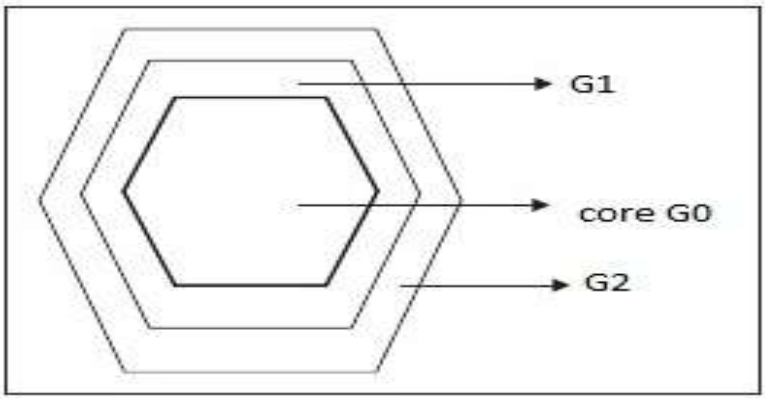


**Figure 3:Dendrimer-based nanotechnological treatmentmodel. The figure depicts the structure of nanotechnologybased dendrimers. Here different layers are added on, in astepwise manner, moving from the core towards theperiphery. These shape up the overall functionality of thesenanosized vehicles for drug coupling and its subsequentdelivery. Each successive layer of branching units constitutesa new generation (g) with a specific number in thedendrimer series.**

**Table 3:dendrimer based drug delivery systems for anti-tubercular therapy.**

| Drug | Formulation | *Mycobacterium species* | Effects | References |
|---|---|---|---|---|
| Rifampicin | Manosylated dendrimer | *Mycobacterium tuberculosis* | Biocompatibility and site specific delivery | 24 |
| Rifampicin | PEGylated poly(propylene imine) | *Mycobacterium tuberculosis* | Increased drug loading capacity, reduced drug release rate and haemolytic toxicity | 25 |

**2.4Solid lipid nanoparticles (SLNs)**

SLNs are other promising carrier systems fordrug delivery applications. Their size ranges from50 to 1000 nm. They are composed of lipids andsurfactants. Lipids used are solid at room temperature and include fatty acids, steroids, triglycerides,partial glycerides and waxes.[26]

Phosphatidyl choline and sodium cholate are the two most common emulsifiers used for stabilizing the lipid dispersion. In case of extra pulmonaryTB, lymphatic system is considerably affectedleading to adversity of immune response. SLN systems are particularly helpful in such situations asthey can effectively deliver the drug formulationto the remote lymphatic system. These drug carriers are prepared by ultrasonication, high-pressure homogenization, high-shear homogenization, solvent injection and solvent emulsification evaporation. SLNs possess unique features such as small size,large surface area, high drug loading capacity andgood bioavailability. As lipid matrix is made fromphysiological lipids, therefore the risk of systemictoxicity is significantly reduced.Various researches have shown the significant role of SLNs in ATD delivery. Shelf life ofencapsulated anti-tubercular dugs (ATDs) such as isoniazid, rifampicinand pyrazinamide was increased to 8 days inplasma and 10 days in organs as compared tocommercially available free drugs (1-2 days). Moreover, five oral doses of SLN-loaded drugs possessa therapeutic effect equivalent to 46 daily dosesof free drugs. Thus, SLN-loaded drugs reducedthe dosing frequency and increase the bioavailability. High dose of isoniazid can result in hepatotoxicity. In recent studies it has beenrevealed that isoniazid when coated with SLNshowed high entrapment efficiency (69%) andprolonged circulation time, thus reduces the riskof hepatotoxicity.[27] The attempts depictingvarious SLN-mediated drug deliveries are summarized in **Table 4**.

**Table 4:SLN's mediated drug delivery for TB.**

| Drug | Formulation | *Mycobacterium species* | Effects | Animal model | References |
|---|---|---|---|---|---|
| Rifampicin, isoniazid and pyrazinamide | Slns prepared by emulsion solvent diffusion | *Mycobacterium tuberculosis* | Reduced dosing frequency | Mice | 28 |
| Rifabutin | Mannose coated slns | *Mycobacterium tuberculosis* | Sustained delivery, reducedside-effects | - | 29 |

**2.5. Nanosuspensions**

A nanosuspension is commonly defined as acolloidal dispersion of particles in the nanoscale.For drug delivery purpose, it is normally employedin the cases wherein the drug is poorly soluble inwater as well as in the organic solvents. In a comprehensive review, Patel and Agrawal[30] havediscussed about the engineering of nanosuspension systems with respect to their release properties thatimpart exceptional drug delivery potential to

them.Nanosuspension ensures overall efficient absorption and better biodistribution of the drugmolecules. During the formulation of a nanosuspension, the crystalline particles of the drug areconverted into amorphous form.Various parameters such as particle size,charge distribution and drug dissolution velocitycan also be effectively and easily monitored as wellas suitably modified to suit a particular kind of drugdelivery mechanism by the use of nanosuspension[31]. Thus, nanocrystalline clofazimine is aseffective as liposomal clofazimine in reducingbacterial loads in the liver, spleen and lungs of*M. Avium* infected mice. This intravenous therapy by nanosuspension is a boon for evading the mycobacterial infections. As ATD can produce serious side-effects, this drug delivery route holds immensepotential for TB treatment.

### 2.6. Nano emulsions

Nanoemulsions represent a stable thermodynamicmixture of two immiscible liquids which arecombined with the help of surfactant moleculesto behave as one phase.[32, 33]In a significantreview article, Ahmed et al.[34] have comprehensively illustrated the use of rifampicin-based nanoemulsions for TB treatment. They have elaborated the critical design features such as viscosity,solubility and chemical interaction ability for nano emulsion design to become optimized drug deliveryvehicles. It has been successfully used for the killingof TB germs at low dosage, and there is hardly anyrisk of toxicity or side-effects. Few examples of nanosuspensions and nanoemulsions based systems are quoted in **Table 5**.

**Table 5:Nanosuspensions and Nanoemulsions based systems for ATD's delivery.**

| Drug | Formulation | *Mycobacterium species* | Effect | Animal model | Reference |
|---|---|---|---|---|---|
| Clofazmine | Nanosuspensions by high pressure homogenization | *Mycobacterium avium* | Reduce bacterial load in lungs, liver and spleen | Mice | 35 |
| Resazurin | O/w emulsions | Anti-microbial | Increased uptake by cells | - | 36 |

### 2.7. Niosomes

Niosomes are the nanosized, nonionic sac likestructural analogues of liposomes but theyhave some additional advantages over liposomes.These molecules are amphipathic molecules thatcan be stabilized using surfactants[37]. Till date TB treatment using niosomes has been performed using the conventional ATDs isoniazid,rifampin and pyrazinamide. Niosomal nanoparticles are immensely helpful in ensuring somecritical parameters for optimum drug bio-distribution in the living systems. These enable estimationof surface charges of the drug particles usingzeta potential technology, the extent of absorption of the drug molecule with the carrier using spectroscopic techniques, particle size of the drug formulation using transmission electron microscopy(TEM),better and smoother delivery of the drug involvedto the requisite sites. Their use has particularlyrevolutionized the site-specific delivery of the drugand significantly reduced the systemic toxicity ofthe drug delivered, TB in particular, by reducing theside-effects to almost nil, also making the treatmentmore accessible[38]. Few examples of niosome based systems for conventional ATD's are quoted in **Table 6**.

**Table 6:niosome based systems for conventional ATD's.**

| Drug | Formulation | *Mycobacterium species* | Effect | Animal model | Reference |
|---|---|---|---|---|---|
| Rifampicin | Niosomal delivery to lymphatics | *Mycobacterium tuberculosis* | Targeted to lymphatic system | Wistar rats | 39 |
| Isoniazid | Niosomes by reverse phase evaporation | *Mycobacterium tuberculosis* | Inhibits mycolic acid synthesis | Mice | 40 |
| Rifampicin and gatifloxacin | Niosomes by reverse phase evaporation | *Mycobacterium tuberculosis* | Greater inhibition | - | 41 |

## 2.8. Carbon nanotubes

Carbon nanotubes are the tubes with lengths of severalmicrometers and cross-sectional diameter in therange of 1-100 nm(**Figure 4**). These are of two main types:single-walled and multi-walled. They can be functionalized with a number of different chemicalmoieties coupled to their surface and possess wideapplications[42]. Moreover, carbon nanotubes can behave in bothmetallic and nonmetallic manner, thereby increasing their biochemical utility manifold. Groups suchas bioactive peptides, proteins and nucleic acids canbe coupled to their surface to make their compounds/moieties more easily available to cells and organs.[43]

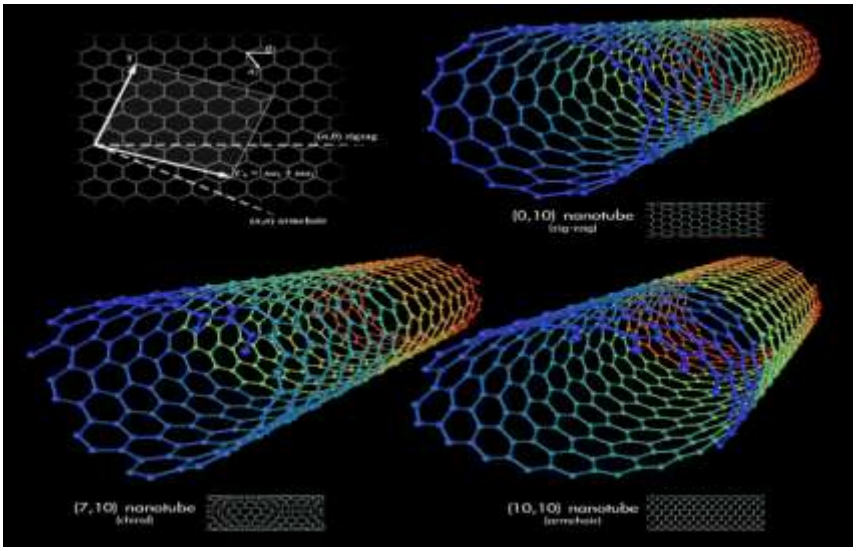


**Figure 4: Types of carbon nanotubes**

## 2.9. Quantum dots

Quantum dots are tiny semiconductor particles (**figure 5**)generally no larger than 10 nm that can be madeto fluoresce in different colours depending on theirsize[44]. They can be very good fluorophores considering their wide spectrum of emission,spanning a wide range of wavelengths. This waythe detection and estimation of TB-infected cellscan be made faster, accurate and effective.

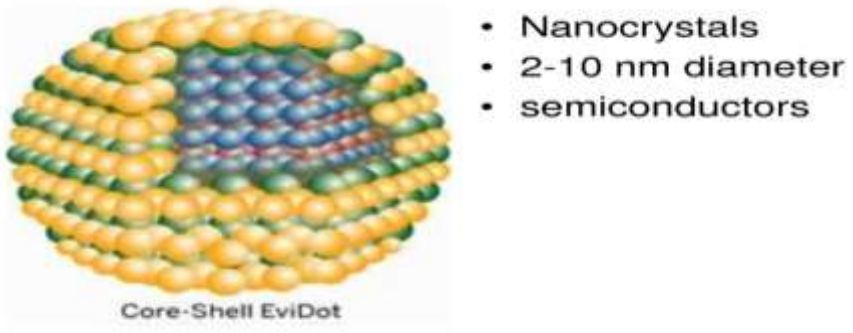


**Figure 5:Schematic presentation of Quantum Dots**

### 2.10. Aerosolic nanoparticles

Aerosolic nanoparticles are a suspension of nanoparticles in dry powdered aerosol form. They areused for the development of nanoparticles aspotential drug delivery molecules that can beinhaled and treat the subsequent pulmonary infections. TB being one of such respiratory infectionshaving multidrug resistance can be therefore veryefficiently dealt with the use of nanoparticles.[45]Using aerosolic nanoparticles efficient detection and treatment of the TB is almost sure to be achievedwith much less systemic toxicity.Inhalable nanoparticles stand better chances ofmucosal adherence, particle(s) delivery and hence netdrug delivery to the lungs.[46] PLG nanoparticles co-encapsulating rifampicin, isoniazid and pyrazinamidewere administered by the aerosol route to guinea pigs. Upon aerosolization, the mass median aerodynamicdiameter (MMAD) was found to be 1.88 µm suitable for deep lung delivery. A single nebulization of theformulation to guinea pigs was able to maintaintherapeutic drug concentration in the plasma for 6-9days and in the lungs for 9-11 days. There was asignificant improvement in the half-life, meanresidence time and relative/absolute bioavailability ofencapsulated drugs compared with free drugs.[47]Repeated administration of the formulation failed toelicit hepatotoxicity as assessed on biochemical basis.In M. tuberculosis H37Rv infected guinea pigs, 5nebulized doses of the formulation spaced 10 daysapart, resulted in undetectable colony forming unit in the lungs replacing 46 conventional doses. This was the firstreport of PLG nanoparticles as an inhalable ATDcarrier. The advantage of the system over inhalablemicrospheres was clear-cut; it was possible toco-administer three ATDs encapsulated innanoparticles whereas, respiratory delivery with microparticles was restricted to one or twodrugs; and secondly, the reduction in mycobacterialload in the lungs was better in case of respirable nanoparticles compared with microparticles. Further, upon nebulization of lectin-functionalized PLG nanoparticles to guinea pigs, therapeutic drugconcentrations were maintained in the plasma for 6-10days and in the organs for 15 days organs. Most of thepharmacokinetic parameters were enhanced comparedwith uncoated PLG nanoparticles and free drugs.Most importantly, when nebulized to TB-infectedguinea pigs every fortnightly, 3 doses of theformulation produced undetectable colony forming unit in the lungs aswell as spleens. The series of experiments provedthat 46 conventional doses could be reduced to 5nebulized doses of PLG nanoparticles and further tojust 3 doses with lectin-PLG nanoparticles. Few examples of Aerosolic nanoparticle based system for TB therapy are coated in **table 7**.

**Table 7:Aerosolic nanoparticle based system for TB therapy**

| Drug | Formulation | *Mycobacterium species* | Effects | Animal model | Reference |
|---|---|---|---|---|---|
| Rifampicin | Plga carrier inhalational drug delivery | *Mycobacterium tuberculosis* | Sustained and targeted delivery to lungs | Rat | 48 |
| Rifampicin | Wheat germ agglutin coated plga | *Mycobacterium tuberculosis* | Reduce dosage frequency | Guinea pig | 49 |

### 2.11. Oral Nanoparticle based Drug Delivery Systems

Main research interest nowadays is focused onmycobacteriology, which tested the feasibility of usingATDs in nanoparticle based controlled deliverydevices. Three frontline ATDs, i.e. rifampicin,isoniazid and pyrazinamide were co-encapsulated Poly (DL-lactide-co-glycolide) nanoparticles (PLG-NP), prepared by the doubleemulsion and solvent evaporation technique. Theparticle size ranged from 186-290 nm with a drugencapsulation efficiency of 60-70% for all the drugs.Particle size distribution homogeneity was indicated by a polydispersity index of 0.38. The formulationwas evaluated for its in vivo pharmacokinetic and pharmacodynamic potential at therapeutic drug doses,i.e. rifampicin 12 mg/kg + isoniazid 10 mg/kg +pyrazinamide 25 mg/kg body weight. Following asingle oral administration of drug loaded PLG-NP tomice, the plasma drug levels were maintained abovetheir minimum inhibitory concentration (MIC90) for6-9 days in the plasma and in organs (lungs, liver andspleen) for up to day 9. However, free drugs werecleared from the plasma and organs within 12- 24 h oforal administration. It was also demonstrated that oraldosing with the PLG formulation at every $10^{th}$ day didnot result in progressive drug accumulation in the tissues. Thechemotherapeutic evaluation of freedrugs administered daily (46 doses) and drug-loadedPLG-nanoparticles administered every 10 days (5doses) orally to *M. tuberculosis* infected mice,showed no detectable tubercle bacilli compared with abacterial load of nearly 4.8 log cfu in lungs/spleen ofuntreated mice[50]. Similar findings were observed in a higher animal model, i.e. guinea pigs.[51]

The WHO recommends the addition of the bacteriostatic drug ethambutol, to the intensive phaseof chemotherapy. Hence, the chemotherapeuticpotentialofPLG-nanoparticleencapsulatedethambutol, when co-administered with the other 3encapsulated frontline ATDs, was evaluated.Following a single oral therapeutic dose of ATD-loaded PLG nanoparticles to mice, the MIC levelswere maintained in the plasma for 3, 6 and 8 days incase of ethambutol, rifampicin and isoniazid/pyrazin-amide respectively. In the tissues, RIF, isoniazid andpyrazinamide were detected till day 9 as previouslyreported[52], while ethambutol was maintained till day7. Free drugs, on the other hand, were not detectablein the plasma beyond 12 h and in the tissues beyond24-48 h of oral administration. Hence, the ATD-loaded PLG nanoparticles were administered to *M.tuberculosis* infected mice at every $10^{th}$ day, whilefree drugs were administered daily. There was asignificant reduction in bacterial load in the 3-drugcombination treated groups at 4 weeks post-chemotherapy. However, there were no detectable colony forming unit(<1.0) in those groups where ethambutol was supplemented to the 3-drug regimen, demonstratingthe potential of the 4-drug combination to shorten theduration of treatment.[53] Thus, with the 4-drugcombination in PLG nanoparticles, it was possible toimprove the drugbioavailability, to reduce the dosingfrequency and to reduce the number of drug doses.Potential mode of entry of PLG-nanoparticles can bethrough M cells, normal epithelial cells or byparacellular route. Though particles in nano-range have been shown to use a transcellular or paracellular route. However number of reports demonstrate theiruptake via membrane epithelial cells.[54]

Nanoparticles can be also targeted to specific sitesby tagging them with suitable ligands. Attempts havebeen made to make PLG-nanoparticle uptake moreeffective by functionalizing them with variouslectins[55]. The nanoparticulate system was further improved by the addition of lectin, a mucosal ligand,to the PLG nanoparticles. Wheat germ agglutinin (WGA) is a commonly occurring plant lectin having low immunogenicity. The receptors for WGA aredistributed on intestinal/respiratory epithelium, thusfavoring its use for oral as well as aerosol drugdelivery. The sustained release profile andpharmacokinetics of all the ATDs was improvedsignificantly as the drugs were detectable in thetissues till day 15 in case of thelectin coated formulation against day 11 in case of the uncoatedformulation. In *M. tuberculosis* H37Rv infected guineapigs, 3 oral doses of ATD loaded lectin PLG-NPspaced 15 days apart resulted in undetectable colony forming unitagainst 46 conventional doses of oral free drugs.The efficacy of the PLG formulation was alsoassessed in animals infected via the aerosol routebecause the latter is the natural mode of acquiring TB.In guinea pigs infected via the aerosol route, 5 oraldoses of ATD loaded PLG-NP and 46 doses of freedrugs still proved to be equiefficacious.[56]This furtherstrengthened the concept of controlled release ATDdelivery systems.Few examples of oral(PO) nanoparticles are coated in **table 8**.

**Table 8:Oral(PO) nanoparticles, alginate and polymeric micelles for TB therapy.**

| Drug | Formulation | *Mycobacterium species* | Effects | Animal model | References |
|---|---|---|---|---|---|
| Rifampicin, isoniazid and pyrazinamide | Oral nano particles | *Myc*obacterium tuberculosis | Sustained release | Mice | 57 |
| Isoniazid, rifampicin, pyrazinamide | Alginate based nanoparticle | *Myc*obacterium tuberculosis | Increase in bioavailability | Guinea pigs | 58 |
| Rifampicin | Polymeric micelles | *Myc*obacterium tuberculosis | Decreased pill burden | - | 59 |

## 2.12. Alginate based Drug Delivery System

Alginic acid is a natural co-polymer of glucuronicacid and mannuronic acid (**Figure 6**) Alginate is alreadyin clinical use for the supportive treatment for refluxesophagitis. It has found applications as a binding anddisintegrating agent in tablets, a suspending andthickening agent in water-miscible gels/lotions/creams and as a stabilizer for emulsions.[60]

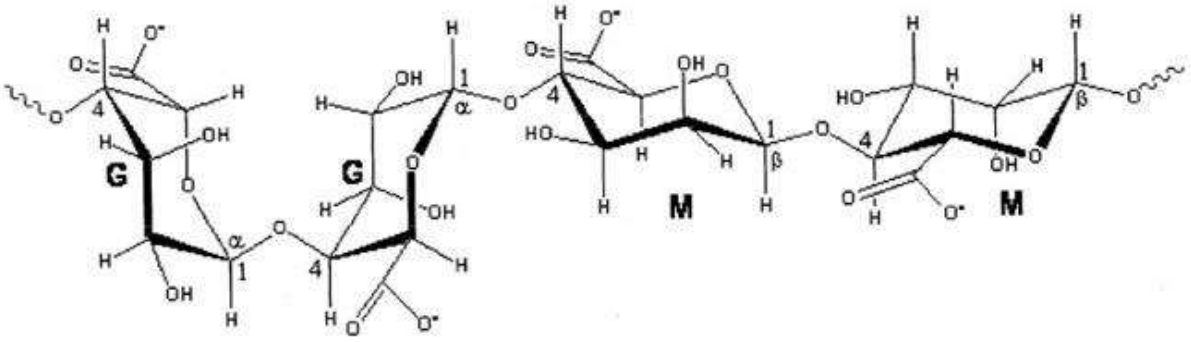


**Figure 6:Alginic acid: A natural copolymer of mannuronic acid and glucuronic acid.**

Severalattributes make alginate an ideal drug deliveryvehicle. These include – (i) a relatively high aqueousenvironment within the matrix; (ii) adhesiveinteractions with intestinal epithelium; (iii) a mildroom temperature drug(s) encapsulation process freeof organic solvents; (iv) a high gel porosity allowinghigh diffusion rates of macromolecules; (v) the abilityto control this porosity with simple coating procedures using polycations; and (vi) biodegradationof the system under physiological conditions. Hence,it is not surprising that alginate has been used as acarrier for the controlled release of antibioticsincluding ATDs[61]. Following the encapsulation of RIF, INH and PZAin alginate microspheres and oral administration toguinea pigs, therapeutic drug concentrations could bemaintained in plasma for 4-5 days and in organs for7-9 days. Weekly treatment with the formulationresulted in complete bacterial clearance in organs ofinfected guinea pigs after 8 oral doses, as did the dailyoral administration of free drugs. A few refinementsin the methodology with the inclusion of chitosan,resulted in a system which was better than the simple alginate system in terms of drug encapsulation/loading, pharmacokinetics and chemotherapeuticefficacy. The most important observation was theability of the alginate-chitosan system to document atherapeutic benefit with just half therapeutic doseadministered weekly. Further, alginate-chitosannanoparticles have also been developed in which theconsumption of polymers has further been reducedbesides maintaining the advantages of nanoparticles.The formulation, which uses 7.5-fold less amount ofpolymer compared with the alginate formulationsdiscussed above, can be administered by the oral routeor nebulized. A single oral administration of theformulation could maintain therapeutic drugconcentrations in the plasma/organs of mice/guineapigs for 2 weeks. An almostsimilar

profile was obtained by the aerosol route inguinea pigs. There was a total clearance of bacillifollowing 6 weeks of chemotherapy comprising of 3nebulized doses of the formulation.[62]Few examples of Alginate based Drug Delivery Systemare coated in **table 8**.

**2.13. Micelles**

As a result of self assembly, amphiphilic polymers give rise to thepolymeric micelles in water. Micellar shell is formed due to the contactof hydrophilic blocks with the aqueous medium, assisting the solubilization of amphiphile in water and stabilizing the aggregate. Conversely,hydrophobic blocks make the inner micellar core which facilitates thesolubilization of poorly water-soluble drugs[63]shielding them fromchemical and biological degradation. These micelles can be mademore lipophilic materials to improve the penetration of incorporateddrug into the pathogen, and its antibacterial activity against*Mycobacterium.*

Commercially available and FDA-approved poly(ethylene oxide)–poly(propylene oxide) (PEO–PPO) block copolymers (linear poloxamers and branched poloxamines) are amongst the majority of importantmicelle-forming materials.[64]Preliminary studies that explored the solubilization of RIF within polymeric micelles of a range of linear andbranched PEO–PPO with a broad spectrum of compositions illustrated a minimal solubilization effect (∼2-fold). These observations propose that the size of the micellar core strongly restricts the encapsulationof the very bulky RIF molecule. Other amphiphilic block copolymers synthesized by linking mono and bifunctional PEG precursors of different molecular weights with poly(ε-caprolactone) (PCL) enabled the finetuning of the HLB and the amplification of the micellar core, improving the solubilization extent by 5- to 7-fold.[65]Jiang and co-workers synthesized thermo-responsive poly(ε-caprolactone-coglycolide)–poly(ethylene glycol)-poly(ε-caprolactone-co-glycolide) (P(CL-GA)–PEG-P(CL-GA)) smart block copolymers with micelle-forming and gelation properties.[66]The sol–gel transition temperature was fine tunedby changing the GA/CL ratio and the length of the hydrophobic segments.RIF-loaded (2 mg/mL) 25% gels were used to characterize the in vitrorelease profile of the matrices over time; the release was sustainedover 32 days. Although, these micellar systems did not show a substantial enhancement in the solubility of the drug, they could find applicationin the development of a drug depot system for the sustained release ofthe drug. To prolong the delivery of RIF, drug-loaded stereocomplex micelles were formed by the particular assembly of enantiomericpoly(ethylene glycol)–poly(L-lactide) (MPEG-PLLA) and poly(ethyleneglycol)-poly(D-lactide) (MPEG-PDLA) block copolymers in a 1:1 ratio ofL-PLA- and D-PLA-containing block copolymers[67].Loading capacityand encapsulation efficiency of RIF in the stereo complexes was higherthan in the enantionerically pure micelles. Drug delivery experiments*in vitro* illustrated a fast initial release (50% after 4–8 h) and a more moderated one (100% after 48 h) at later times. Moreover, the invitro drugrelease could be regulated by the molecular weight of the polymer. Wuet al. developed PLA-modified chitosan oligomers competent of aggregating in water to form spherical micelles having sizes between 154and 181 nm.[68]Entrapment of 10% RIF into the nanocarriers resulted in core expansion to sizes in the range of 163–210 nm. *In vitro* release experiments illustrated a burst effect (35% within 10 h) followed bysustained release until day 5. To achieve higher effectiveness and longeranti-TB activity while limiting the toxic effects, Silva et al. synthesizedINH-poly(ethylene glycol)–poly(aspartic acid) conjugates that sustain the release of the drug over time.The micelle-forming pro-drugshowed a 5.6 fold increase in anti-tubercular activity against*M. tuberculosis in vitro* in comparison to the free drug. The mechanismproposed principally involves micelle uptake and intracellular releaseof the drug following the hydrolysis of the linkage. The identical synthetic pathway was pursued in order to encapsulate PZA and RIF. Dueto relatively low CMC values (5 × 10−4–5 × 5−10 mg/L) micelles werestable *in vitro*. The size and distribution of these micellar nanoparticles were found to be 78 nm, 84 nm and 99 nm, respectively, for PZA, INHand RIF conjugates and level of the conjugated drug was in the range of65.0–85.7%.Size of the micelles would avoid renal filtration, increasing the residence times in the blood stream. Furthermore, a strongeranti-mycobacterial activity was apparent. To conquer resistance, Jin andcollaborators designed INH lipid derivatives. The new amphiphilic molecules formed monolayers at the air/water interface. The aggregationbehavior was closely related to the character of the hydrophobic tail.Flexible medium-long tails formed nano-sized vesicles. On the contrary,short lipid tail-derivatives displayed weak hydrophobic interactions andthey did not self-assemble. Molecules with very long tails led to the formation of crystal-like structures. The promising antibacterial activity ofthese micelles was demonstrated against *Mycobacterium* due to a morelipophilic structure that improved the penetration of the drug into the pathogen.Few examples of micellar Drug Delivery System are coated in **table 8**.

### 2.14. Injectable Nanoparticle based Drug Delivery Systems

The subcutaneous and intramuscular routes provide bioavailability profiles close to the intravenous route.An important attribute of PLG nanoparticles was a High chemo therapeutic efficacy following 41 subcutaneous administration . A single injection ofdrug loaded PLG-nanoparticles resulted in sustaineddrug levels in the plasma for 32 days and in theorgans for 36 days. There was a complete bacterialclearance from the organs of TB infected mice with asingle dose of the formulation thereby proving itsbetter efficacy compared with injectable PLG microparticles. PLG polymers are biodegradable, biocompatibleand non-immunogenic in humans.[69, 70] Therefore thesepolymers can be repeatedly administered withoutadverse effects. PLG has a long history of safe use inhumans as sutures, bone replacements and dentalrepairs etc. They have been approved by FDA, USAfor human use through subcutaneous route. A longterm depot delivery system of an LH-RHsuperagonist, leuproretin acetate is currently availablein the third market.[71]These observations furthersupport the application of PLG-based nanotechnologyfor mycobacterial infections.

## 3. Conclusions

By utilizing nanotechnology, synthetic and naturalpolymer-based controlled release ATD nanomedicine formulations have been developed, encapsulating key first-line as well as second-line ATDs. They are a more convenient alternative to "New Drug Discovery" which is time consuming (launch of any new molecule takes almost 20–30 years), and costly (about 100 billion dollars/molecule).Packaging or remodeling of existing ATDs demonstrating significantanti-mycobacterial potential with low MIC, using suitable nanostructured carrier systems tends to address multiple issues like solubility,stability, permeability, drug degradation or interaction, and severe adverse effects. The improved drug bioavailability and therapeutic efficacy were witnessed even at subtherapeutic doses. In addition to a lower effective dose, the period of chemotherapycan also be shortened by use of nanotechnology based products. Nanomedicine may be the long-sought solution for improving patient compliance inTB chemotherapy. A major breakthrough expected out of these nanoantibiotic systems entrapping ATDs within nanocarriers is their capacity to enter into andact on the *Mycobacterium* by a variety of mechanisms. Thus it may be concluded that the nanosystems offer a variety of advantages over the conventional antitubercular therapy and would be of greater applicability in near future.

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