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Review Article

Nanoparticles as a Novel Drug Delivery System in Tuberculosis: Comprehensive Review on Formulations, Pre-clinical studies and Patent

Raj Kumar Mandal[1*], Sneha[2], Sonia[2], Jaspreet Singh[2] and Amanpreet Kaur[2]

[1]*I.S.F College of Pharmacy (ISFCP), G.T Road, Moga, Punjab, India (142001).*
[2]*Department of Pharmaceutical Sciences, Government Polytechnic College, Patiala, Punjab, India (147001)*

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ABSTRACT

Background: Tuberculosis is a serious world health concern with millions affected annually. The development of Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis strains shows how the development of novel therapy approaches is highly needed. Nanoparticles have emerged as a promising drug delivery platform due to their potential for targeted delivery, sustained release and enhanced intracellular accumulation within infected macrophages while reducing systemic toxicity.
Objectives: This review aims to explore the formulation and structural aspects as well as compositional properties of an effective nanoparticle based drug delivery system of TB treatment, pre-clinical studies and patent developments. It considers their ability to enhance drug bioavailability and efficacy along with targeting performance and experimental difficulties when utilizing its effect on intervening commercialization and translation problems.
Methodology: PubMed analysis, Google Scholar analysis, Scopus analysis, Google Patents, Clinicaltrials.gov, etc. were the sources of the relevant literature published between 2015 to 2026. The review includes the classification, structure and composition of nanoparticles. Further it includes pathogenesis guided drug delivery approaches, patents, formulations and pre-clinical trials.
Key Findings: Nanoparticles enhance pharmacokinetics, drug stability and macrophage targeted delivery. Patents & pre-clinical studies highlight innovations in polymer selection, encapsulation efficiency and sustained-release formulations. Despite promising results, challenges remain in large-scale production, regulatory approval and cost-effective accessibility.
Conclusion: Nanoparticles represent a transformative approach in TB therapy, bridging formulation innovation with pre-clinical applicability. Continued research and development are essential to realize their full potential in combating drug-resistant TB.

Introduction

Tuberculosis (TB), is caused by *Mycobacterium tuberculosis (M. tuberculosis)* remains a major global health burden with an estimated 10.6 million cases and 1.3 million deaths every year. Multidrug-Resistant

Tuberculosis (MDR-TB) and Extensively Drug-Resistant Tuberculosis (XDR-TB) as comprising 3-4% of new and 18-21% of retreated cases respectively which causes a further complicated treatment outcome. The standard therapy is made of rifampicin, isoniazid, ethambutol and pyrazinamide which are expected to last 6-12 months although are characterized by low adherence, hepatotoxicity and irregular pharmacokinetics. Crucial drawback is poor delivery of drugs into the cell interiors since; *M. tuberculosis* can survive in macrophages because it prevents phagosome-lysosome fusion and acquires an inactive form. It is estimated that among administered drug only 30-50% of the amount gets to intracellular compartments resulting in subtherapeutic levels [1]. Novel Drug Delivery System (NDDS) which are usually between 10-500 nm, are more advantageous in terms of drug stability, permeability as well as controlled release. Functionalization of surfaces with ligands like mannose also allows targeting of the cells by the CD 206 receptors which enhances intracellular accumulation of the drug massively. Research has indicated that nanoparticle formulations have a 2-6 fold increase in intracellular drug concentrations over conventional drugs [2]. Nanoparticles significantly improve pharmacokinetic parameters including bioavailability and half-life. Systems based on PLGA delivers 7-14 days of sustained release whereas lipid-based carriers including SLNs and NLCs, increase bioavailability by 3 to 5 fold. Formulations of inhalable nanoparticles allow 8-10 fold higher pulmonary drug concentration which increases local delivery. In preclinical experiments, improved therapeutic efficacy is provided such as 2-3 log CFU diminution when in contrast with free drug preparations and diminished systemic toxicity. Nevertheless, such issues as mass production, reproducibility, regulatory authorization and safety in the long run are still obstacles to clinical translation [3].

Classification, Structure & Composition

Structural features

The biological performance, efficiency of drug delivery and success of therapy of TB is highly determined by the structural properties of nanoparticles.

*Corresponding author: Raj Kumar Mandal; U.G Scholar, I.S.F College of Pharmacy (ISFCP), G.T Road, Moga, Punjab, India (142001).

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Parameters such as particle size, surface charge (zeta potential), morphology, surface functionality and internal structure are important parameters that influence macrophage uptake, drug release and stability. Particle size is a critical determinant with 100-300 nm considered optimal for macrophage uptake. Particles below 100 nm can be quickly cleared and particles larger than 500 nm present a lowered internalization. The uniformity of the distribution of size should be under 0.3 as polydispersity index (PDI). Surfaces of ±20 to ±40 mV stability leads to colloidal stability and positive charge leads to cellular uptake but results in cytotoxicity. The behaviour depends on the morphology where uniform morphology has been shown to be preferred, however, rod-like morphology can enhance adhesion and circulation. The CD206-receptors can be targeted by surface functionalization with ligands including mannose which increases the intracellular uptake [4,5]. PEGylation also enhances circulation with the help of immune recognition. The mechanism of drug release is dependent on internal architecture and matrix systems are capable of drug release through diffusion control whereas core-shell offers sustained release. Porosity increases the drug loading capacity with mesoporous nanoparticles having encapsulation factors of 85-95% compared to the conventional 60-75% [6].

Composition and Materials

Physicochemical properties, biocompatibility, drug loading and therapeutic performance of nanoparticles in the treatment of TB highly depends on their composition. Polymers, lipids, surfactants and inorganic components are also common materials that are used to maximize the delivery system. Nanoparticles in the form of polymers and especially PLGA are intensively investigated because of biodegradability and regulatory acceptability. PLGA systems demonstrate 70-90% encapsulation efficiency and release of up to 7-14 days and the ability to increase bioavailability by 3-5 folds. Chitosan nanoparticles have a high encapsulation efficiency of 65-85% an increased muco-adhesion and cellular uptake with increased stability and controlled release due to the addition of alginate. NLCs and SLNs are lipid-based nanoparticles which enhance solubility and stability. SLNs measure 50-200 nm and 40-80% drug loading where NLCs exhibit 85-90% drug loading efficiency with prolonged release (24-72 hours). Such systems increase 3-5 fold lymphatic uptake resulting in bioavailability [7].

Liposomes allow the encapsulation of hydrophilic and lipophilic drugs with 60-85% efficiency and 2-4 fold higher retention time and less toxicity. Nano-emulsions (20-200 nm) increase the drug solubility and dissolution

at 2-3 folds, but the stability is a drawback. Nanoparticles are made more stable with the help of surfactants like Tween 80 and more uniform with the help of stabilizers like PVA and the variation in size is usually less than 10%. Antimicrobial properties and high drug loading (>90%) are provided by inorganic nanoparticles such as silver and mesoporous silica but issues of toxicity remain. Hybrid nanoparticles utilize polymeric systems with lipid systems and a higher encapsulation efficiency of over 85% and enhance the pharmacokinetics of nanoparticles [8].

Pathogenesis and Management of Tuberculosis

TB is a chronic infectious disease because it is able to survive in host cells and avoid immune attacks. It is an obligatory aerobic, acid-fast bacillus with a complicated lipid-rich cell wall that is formed with mycolic acid, arabinogalactan and peptidoglycan that helps the pathogen to survive desiccation, damage by the chemicals and host defence. The bacteria are transmitted by inhaling the aerosolized droplets whereby the bacilli attack the alveolar spaces of the lungs and start to multiply. Pattern recognition receptors, such as Toll-like receptors (TLR2 and TLR4), mannose and complement receptors recognize and internalize *M. tuberculosis* upon entry into alveolar macrophages. In spite of phagocytosis the survivability of the pathogen in the cells is through suppression of phagosome maturation and inhibition of lysosome fusion. Virulence factors affecting this process include lipoarabinomannan (LAM), phosphatidylinositol mannosides (PIMs) and early secretory antigenic target-6 (ESAT-6) that disrupt various intracellular signalling pathways including calcium flux and phosphatidylinositol 3-phosphate (PI3P) formation [9]. Therefore, the bacteria remain in the immature phagosomes which provide a niche inside into which the bacteria replicate. Inside the macrophages, *M. tuberculosis* experiences oxidative and nitrosative stress which are produced by reactive oxygen species (ROS) and reactive nitrogen species (RNS). To counter intracellular survival, the pathogen has antioxidant enzymes like superoxide dismutase and catalase-peroxidase (KatG). It has also been adapted to survive under nutrient limiting conditions taking advantage of host-derived lipids as a form of primary energy by metabolic mechanisms including glyoxylate shunt, facilitating persistence in stressful environments [10]. Infected macrophages produce pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interferon- gamma (IFN-γ) which attract immune cells to the point of infection. This leads to the formation of granulomas which are organized aggregates of infected macrophages, epithelioid cells, multinucleated giant cells and lymphocytes around them. Granulomas have the effect of housing and therefore limiting the infection, but they also form a hypoxic and nutrient-deficient microenvironment which causes bacterial dormancy. This non-replicating persistent infection is controlled by DosR regulon which allows *M. tuberculosis* to stay longer with low metabolic rate. Latent TB infection is the one that is present in the body in form of granuloma as the bacteria held in immunological system and has not been eliminated properly. It is estimated that about 25% of the world population has latent TB and this has been accompanied by a 5-10% lifetime risk of developing active disease [11].

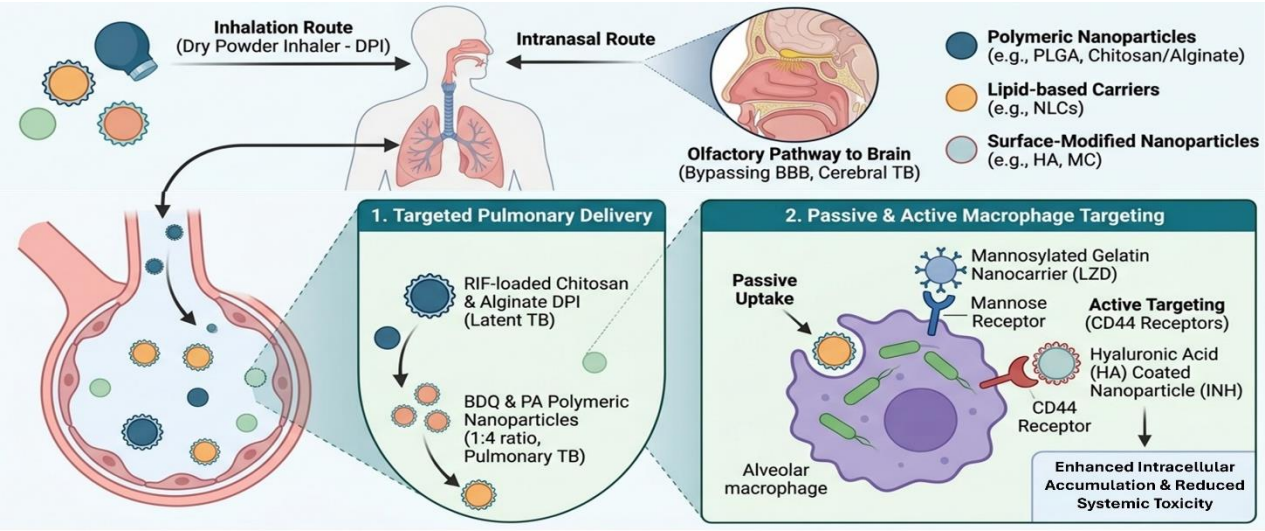

Figure 1: Schematic illustration of targeted nanoparticle delivery systems in tuberculosis, including inhalation, macrophage uptake and CNS targeting routes.

The reactivation is linked to immunosuppressive host states like HIV infection, diabetes mellitus, malnutrition, old age or immunosuppressive therapy. In the case of active TB, the integrity of granuloma is disrupted and caseous necrosis is observed which implies the formation of lipid-rich cellular debris in large quantities. This setting encourages the growth of bacteria and leads to their spread in the lungs and other external locations. Sputum of bacilli spread through coughing as they are released into the airway [12]. Host immune responses include innate and adaptive cells, with the central role of CD4 + T cells mediating the activation of macrophages which is done by the use of IFN-γ. But too much immune activation may lead to tissue damage whereas the regulatory cytokines like IL-10 have a role in immune suppression and persistence of bacteria. TB is treated by a long period of multidrug chemotherapy against both the actively active and dormant bacterial groups. The first-line regimen comprises of rifampicin, isoniazid, pyrazinamide and ethambutol in an intensive phase of 2 months to be followed by a continuation phase of 4 months of rifampicin and isoniazid. The regimen has success rates of over 85% in TB that is sensitive to drugs but it has a variation in the treatment outcome because of differences in patient adherence and pharmacokinetics. Rifampicin has action against DNA-dependent RNA polymerase, inhibits transcription whereas isoniazid inhibits the synthesis of mycolic acids following KatG-activation [13].

Pyrazinamide is used in acidic condition and destabilizes the membrane energetics whereas ethambutol would stop the formation of cell wall by blocking arabinogalactan synthesis. These drugs have negative side effects, such as hepatotoxicity and optic neuritis, though they have been effective which can somewhat impact compliance. MDR-TB which is resistance to rifampicin and isoniazid, necessitates long therapy measures of 18-24 months and the success rate lies between 50-60%. The second-line drugs are fluoroquinolones like levofloxacin and moxifloxacin that inhibit DNA gyrase as well as injectable drugs like amikacin [14]. More recent medicines such as bedaquiline, a drug that inhibits the ATP synthase and delamanid, a drug that inhibits the production of mycolic acid have done better but must be monitored because of possible cardiotoxicity. One of the greatest shortcomings of TB treatment is insufficient penetration of drugs into granulomas and intracellular complexes resulting in subtherapeutic concentration. This has led to the establishment of more specific drug delivery methods such as nanoparticle-based systems to improve intracellular drug concentrations and therapeutic outcome [15].

Host-directed therapies are under investigation as a way of regulating the immune response and promotes bacteria clearance. The use of Agents like metformin stimulates AMP-activated protein kinase (AMPK) that enhance Macrophage activity and lower bacterial count in preclinical research. Other methods are immunomodulators like statins, vitamin D. Vaccination has also been used as a significant preventive measure and the Bacillus Calmette-Guerin (BCG) vaccine has demonstrated effectiveness in preventing severe TB in children but not in adults [16]. New vaccine candidates such as subunit and viral vectors based vaccines are being studied. Inhalable drug delivery systems include pulmonary drug delivery systems which enhance targeting of the drug to the lungs resulting in increased local concentrations and decreased systemic exposure. The innovative developments in the field of molecular diagnostics including nucleic acid amplification tests will allow promptly detecting infection and drug resistance and initiating treatment accordingly [17].

Methods of Preparation

The choice of nanoparticle preparation method depends on the properties of drugs, required size of the particle, efficiency of encapsulation and release behaviour. Popular methods mentioned in the literature are solvent-based and non-solvent-based methods which affect formulation performance. All parameters that directly depend on the method used include particle size distribution, polydispersity index and drug loading capacity. Solvents-based methods entail dissolution of polymer or lipid in organic solvents; then emulsification or precipitation processes are performed, nanoparticles with defined morphology are formed [18]. The method usually results in particles around 50-300 nm with encapsulation efficiencies of 60-90% and varies by factors of formulations. Non-solvent based methods like the ionic gelation method are based on cross-linkers and electrostatic interactions between polymers and cross-linkers and provide mild processing conditions which are appropriate to handle sensitive drugs. The process parameters such as the rate of stirring, the rate of evaporation of solvent, concentration of the surfactant and temperature play a great role in dictating the properties of nanoparticles and their reproducibility [19].

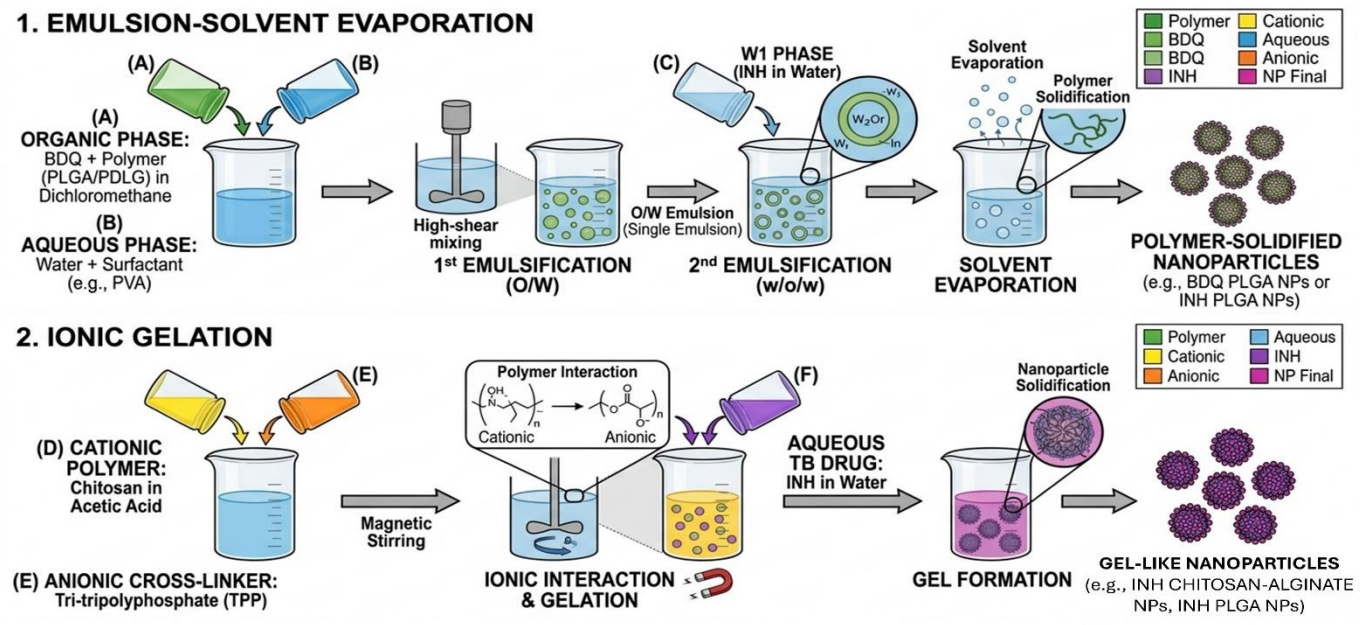

Figure 2: Schematic representation of nanoparticle preparation methods including emulsion-solvent evaporation and ionic gelation techniques.

Emulsion-solvent evaporation

One of the most common methods applied in the production of polymeric nanoparticles is the emulsion-solvent evaporation method which is especially popular in the case of hydrophobic drugs like rifampicin. Under this approach, the polymer and drug are dissolved in a volatile organic solvent completely like dichloromethane, chloroform or ethyl acetate, to create the organic component. The phase is subsequently homogenized under the conditions of high-speed homogenization or ultrasonication into an aqueous phase with stabilizers like polyvinyl alcohol (PVA) or Tween 80 to create an oil-in-water (o/w) emulsion [20]. The size of the droplets used to make the emulsion directly influences the size of the end product nanoparticles which usually vary between 100-300 nm. Achieving a uniform particle distribution, that is, a polydispersity index value less than 0.3 is commonly reported at homogenization speeds of 10,000-20,000 rpm and sonication amplitudes of 40-70%. After the emulsification process, the organic solvent is evaporated with reduced pressure or the particle is stirred in a continuous manner until the polymer precipitates to form solid nanoparticles [21]. Efficiency with regard to encapsulation under this technique is typically 65-90% with regards to drug solubility, polymer concentration and the choice of solvent. An increase in polymer-to-drug percent ratios and low drug solubility in the aqueous phase also leads to better encapsulation. The concentration of the surfactant is also vital; the common concentration of the surfactant is 0.5-2% w/v which is sufficient to stabilize the droplets in the emulsion and avoid aggregation. The issue of temperature regulation of solvent evaporation also matters, since high temperatures can result into high rate of loss of solvents and particle aggregation. Further the solvent content as a residual should be reduced to regulatory limits and in class II solvents, this should be less than 5000 ppm [22].

Double emulsion (w/o/w) solvent evaporation

Encapsulation of Hydrophilic drugs, proteins or peptides into polymeric nanoparticles is achieved mostly using the double emulsion (water-in-oil-in-water) solvent evaporation technique. In this method, the primary emulsification is carried out after which secondary emulsification is done to enhance drug entrapment and stability. First, the hydrophilic drug is dissolved in water phase which is emulsified in an organic phase in which a dissolved polymer like PLGA exists using high-speed homogenization or probe sonication to create a primary water-in-oil (w/o) emulsion [23]. Fine droplet formation is generally achieved by sonication amplitudes of 30-60% over 30-90 seconds. This primary emulsion is then further incorporated into even larger amounts of aqueous phase that has stabilizers like polyvinyl alcohol (PVA) so as to create the secondary w/o/w emulsion. Nanoparticles developed by means of this technique typically measure between 150-400 nm in size and polydispersity index as low as 0.3 with optimum conditions. Efficiency of hydrophilic drugs encapsulation is normally less than

hydrophobic, with a range of 40-75%, as drugs may diffuse into external aqueous surrounding during emulsification [24]. The characteristics of nanoparticles rely on process parameters including the volume ratio of the internal to the external aqueous phase, the concentration of the polymer and the concentration of the surfactants. A more concentrated polymer increases the encapsulation efficiency whereas more than aqueous phase outside can decrease the size of the particles but it can also escalate the drug leakage as well. After creation of emulsions, organic solvent is evaporated with stirring and nanoparticles solidify. Small amounts of solvents are kept within acceptable levels as required by the laws and regulations and the product is safe and stable [25].

Nanoprecipitation

Nanoprecipitation also referred to as the solvent displacement process is a very simple and reproducible process extensively employed in preparing polymeric nanoparticles especially of hydrophobic drugs. This technique relies on the high-speed diffusion of an organic solvent that is soluble in water into an aqueous solution and thus leads to the supersaturation followed by the fixation of the polymer. During this process, polymer and drug are dissolved in a semi-polar organic solvent e.g. Acetone, ethyl or acetonitrile to create organic phase. The solution is subsequently dropwise or injected into an aqueous medium where stabilizers like polyvinyl alcohol (PVA) or poloxamers are present in moderate levels of stirring, usually of 500-1500 rpm [26]. The quick spread of the organic solvent into the aqueous phase results in low quality of solvents which culminates into immediate nucleation and creation of NPs. The characteristics of particles formed in nanoprecipitations are a size of 50-200 nm when the size distribution is narrow with polydispersity index values less than 0.2 when optimal conditions are observed. The encapsulation efficiency usually is between 60-85% and this depends on the solubility of the drug and the concentration of the polymer [27]. Increased concentrations of polymers lead to an increase in the particles size as a result of higher viscosity whereas increased stirring speeds lead to a decrease in the particle size. This solvent is then dried either by over time evaporation or by repeated stirring and leaving behind very little remnants of solvent. This technique is especially ideal with thermolabile compounds and drug molecules that are sensitive to shear because high shear forces are absent. The key factors that influence the formation of nanoparticles are the ratio of solvent to antisolvent, rate of injection, concentration of the polymer and the type of stabilizer. The antisolvent volume should be larger to facilitate diffusion at higher rates and reduced particle size whereas the rate of nucleation should be controlled to avoid aggregation and concentrate on uniform nucleation [28].

Ionic gelation

The process of ionic gelation is neither harsh nor very debilitating method usually applied when preparing nanoparticles out of natural polymers like the chitosan and the alginate polymers. The underlying principle of this technique is determined by the electrostatic interactions between the oppositely charged polymers and the crosslinkers resulting in the creation of a three-dimensional net without solvents. This is achieved by dissolving an amino polymer in an acidic aqueous solution which in most cases contains acetic acid and leads to the process of protonation of the amino groups (-NH3+). The polymer solution is into which the drug is dissolved or dispersed. Dropwise under constant stirring, a crosslinking agent, typically sodium tripolyphosphate (TPP) is added [29]. TPP phosphate groups are negatively charged and react with the positively charged amino groups of chitosan resulting in spontaneous formation of nanoparticles by ionic crosslinking. Particles prepared through an ionic gelation process usually have particle sizes of 100-300 nm with the value of the polydispersity index being below 0.3 in optimum situations. Encapsulation efficiency. This is typically 60-85% and this is based on polymer concentration, drug properties and ratio of crosslinkers [30]. The chitosan concentration causing an increase in particle size and viscosity and the TPP concentration causing an increase in crosslinking density but potential aggregation. A good ratio of chitosan to TPP is another key parameter affecting the properties of nanoparticles and more typically reported ratios have been in the range of 3:1 to 6:1. Stirring between 500-1000 rpm is usually used to maintain a homogenous mixture and particle development. It is especially beneficial in the encapsulation of hydrophilic drugs, proteins and nucleic acids since it is aqueous lacks the use of harsh solvents and maintains biological functionality and structure [31].

Salting-out

Salting-out is a variation of the emulsification process employed in the process of filling the polymeric nanoparticles without applying high temperature and strong shearing forces. This technique works best with thermosensitive compounds and it is grounded on the lower solubility of a water-miscible organic solvent at elevated concentrations of salting-out agents. Under this method the polymer and drug are dissolved in an

organic solvent that is water miscible like acetone. It is then emulsified into an aqueous phase with high levels of salting-out agents (e.g. magnesium chloride, calcium chloride or sodium chloride) and stabilizers. The existence of these salts hinders instant diffusion of the organic solvent into the water layer which means that the formation of a stable oil water emulsion can be created under moderate stirring conditions, normally 500-1000 rpm [32]. After formation of emulsion, the ionic strength of the system may be lowered by addition of large amount of water and this allows rapid diffusion of the organic solvent to the aqueous phase. This causes a polymer to be supersaturated and precipitates to form nanoparticles. The average particle sizes have been found to be around 100-300 nm with polydispersity index value of less than 0.3. The efficiency of encapsulation normally decreases to 60-85% based on drug solubility, concentration of polymer and salt composition [33]. A concentration of high salt concentration enhances stability of emulsions but can be very laborious considering that complete leftover salts have to be washed out. This is done by removal of salts and solvents by filtration or centrifugation followed by purification. The key parameters to consider which affect the properties of nanoparticles are the salt type and concentration used and the ratio of polymer to drug as well as the rate at which the solution is diluted which influence the nucleation, size and stability of the nanoparticles [34].

Supercritical CO_2 extraction

Supercritical fluid technology, especially supercritical carbon dioxide (SC-CO2) is a sophisticated method in the preparation of nanoparticles because it can be used to tune solve qualities, its toxicity is low and the solvent could be easily extracted. Above its critical temperature (31.1°C) and its critical pressure (73.8 bar), carbon dioxide is in the steady state of becoming supercritical with properties in between liquids and gases revealing that it is able to dissolve and transport mass effectively. Methods of preparation that are widely used in the preparation of nanoparticles include Rapid Expansion of Supercritical Solutions (RESS) and Supercritical Anti-Solvent (SAS) [35]. In the RESS technique, a solution containing the drug and the polymer is dissolved under supercritical pressure CO2 and expelled via a nozzle into an area of reduced pressure causing the rapid supersaturation followed by growth of nanoparticles. The SAS system combines the drug and the polymer that is dissolved in an organic solvent which is then loaded into a chamber with supercritical CO2 which is an anti-solvent resulting in fast diffusion of the solvent and the formation of nanoparticles. The particle sizes measured by the SC-CO2 techniques are usually 50-200 nm in size and the index of polydispersity are lower than 0.2 [36]. Efficiency of encapsulation ranges between 60-90% according to the solubility and working conditions. The typical operating pressures are 80-300 bar and the temperatures kept at 35-60°C as well as to keep thermolabile compounds stable. This technique has a significant benefit in the absence of residual organic solvents because CO2 can readily be removed by depressurization. The process parameters like pressure, temperature, flow rate and nozzle design play a significant role in determining the morphology and size distribution of the particle [37].

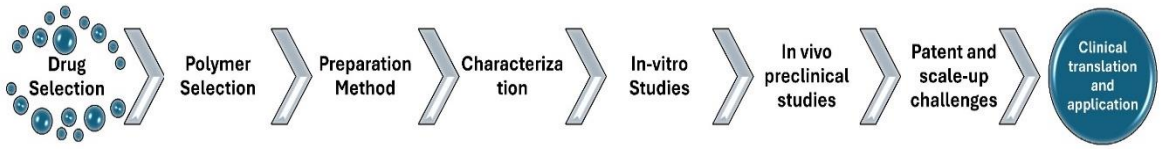

Figure 3: Development pipeline of nanoparticle-based tuberculosis therapeutics from formulation to clinical translation.

Current Status of Nanoparticles in TB

Drug delivery systems based on nanoparticles to treat TB are at advanced preclinical development phase and minimum clinical translation. It has been shown that polymeric nanoparticles, lipid-based systems and liposomal formulations have higher pharmacokinetics and intracellular targeting. Enhancement of bioavailability and sustained release profiles of rifampicin loaded PLGA nanoparticles have already improved 2-5 times in animals models over 10 -14 days. Nanoparticles made by solid lipid and nanostructured lipid carriers have been found to be better absorbed orally and its stability, with a particle size of less than 200 nm. Inhalable nanoparticle preparations are also being explored and are able to attain a high pulmonary deposition and physical proximity of drug delivery. In spite of these developments, large-scale manufacturing issues, reproducibility and regulatory approvals still act as a constraint to clinical use [38].

Granted/Published/Designed patent for TB Nanoparticles

Recent patent cases indicate great novelty in TB drug delivery systems based on nanoparticles in several jurisdictions such as the United States, Europe, as well as India. Some of the formulations mentioned in patents include rifampicin-loaded PLGA nanoparticles, liposomal inhalable systems and chitosan-based macrophage-targeting carriers. Some of the designs are aimed at high efficiency of encapsulation (more than 80%) and long-term release of the drug of more than 7-10 days. Ligand-functionalized nanoparticles which enable targeted delivery and enhanced intracellular uptake are also the focus of the patent filings. Nevertheless, the majority of the patented technologies are still in preclinical or prototype phase and not many of them are turned into the commercial-scale production and realization of the regulatory approval [39].

Table 1: Detailed list of granted patents for the treatment of TB.

Authority	Application No. / CBR / Grant No.	Title	Applicants	Inventors	Filing Date	Published/ Grant/ Approved/ Designed Date	Ref.
Russia	RU2839855 C2	Colloidal silver for enhanced anti-TB bioavailability	Lyubimov G.Y.	Lyubimov G.Y.	Apr. 15, 2024	May 13, 2025	**[40]**
China (CNIPA)	CN11152970 4B	AIE-based antibacterial nano-micelle system	Sun Yat-sen University	Huang X. et al.	Mar. 19, 2020	Mar. 22, 2022	**[41]**
Europe (OEPM)	EP3943070	Long-acting bedaquiline formulation	Janssen Pharmaceutica	Bernini G.Y. et al.	Jul. 13, 2018	Nov. 22, 2023	**[42]**
China (CNIPA)	CN11657065 4B	Phytochemical-gold nanoparticle conjugate	Zhongjing TCM Institute	Khan M.T. et al.	Apr. 21, 2023	Mar. 25, 2025	**[43]**
China (CNIPA)	CN11732344 2B	MnO_2 macrophage-targeted nano-system	Guangdong Medical University	Liao K. et al.	Aug. 30, 2023	May 3, 2024	**[44]**
China (CNIPA)	CN11313398 9B	Long-acting rifampicin nano-formulation	Xi'an Medical University	Li K. et al.	Mar. 9, 2021	Apr. 25, 2023	**[45]**
China (CNIPA)	CN10955005 3B	Dual-drug polymeric nano anti-TB system	Xi'an Chest Hospital	Wu D. et al.	Dec. 12, 2018	Oct. 27, 2020	**[46]**
China (CNIPA)	CN11898719 7B	Heat-stable multivalent TB nano-vaccine	Shandong Medical University	Chong Y. et al.	Oct. 24, 2024	Jan. 24, 2025	**[47]**
China (CNIPA)	CN11507361 2B	TB protein-based nanoparticle system	Ningxia University	Li Y. et al.	Jun 20, 2022	Sep 27, 2024	**[48]**
China (CNIPA)	CN11456990 3	Ultrasound-assisted nano drug delivery device	Chongqing Medical University	Du Y. et al.	Jan 20, 2022	Sep 13, 2024	**[49]**

Formulations for TB Nanoparticles

The nanoparticles formulations in use for treating TB mainly have polymeric nanoparticles, solid lipid nanoparticles and liposomes and nano-emulsions that have first-line drugs including rifampicin, isoniazid and pyrazinamide. Research indicates the sizes of 80-250

nm and encapsulation efficiencies of between 65-90%. The combination-loaded nanoparticles have shown drug release coordination and enhanced pharmacokinetics. The inhalable dry powder formulations of nanoparticles are also in development that exhibits better drug retention and pulmonary deposition than traditional oral dosage formulations [50].

Table 2: Detailed list of under research formulations for the treatment of TB

Drug/API	NP Type	Polymer	Route	Indication	Key Remark	Ref.
RIF	Polymeric NP	Chitosa-Alginate	Inhalation (DPI)	Latent TB	Sustained release in lung & macrophage fluid	**[51]**
LZD	Protein NP	Mannosylated Gelatin	Inhalation	Pulmonary TB	Size: 197-298 nm; EE: 51-56%	**[52]**
INH	Polymeric NP	Mannose-Chitosan, HA	Inhalation (DPI)	Pulmonary TB	Dual targeting: CD206 & CD44	**[53]**
BDQ + Q203	Polymeric NP	PDLG	Inhalation	Pulmonary TB	Magnetic targeting + ATP inhibition	**[54]**
BDQ + PA	Polymeric NP	PLGA	Inhalation (DPI)	Pulmonary TB	Synergistic effect (1:4 ratio)	**[55]**
INH + RIF	Mucoadhesive NP	Chitosan	Nose-to-brain	Cerebral TB	Bypasses BBB	**[56]**
INH + RIF	Polymeric NP	Norbornene-PEG	Oral	TB	Enhanced antimycobacterial activity	**[57]**
RIF / INH	Inorganic NP (MSNP)	PEI / Cyclodextrin	-----	Host-directed	High loading & efficacy	**[58]**
INH + MFX	Polymeric NP	PLGA	-----	MDR-TB	Dual-drug synergy	**[59]**
INH + RIF	Polymeric Micelles	PEG-PLA	-----	TB	High efficacy, low hemolysis	**[60]**
CFZ	Hybrid NP	-----	Intranasal	Cerebral TB	Enhanced brain delivery	**[61]**
PZA	Polymeric NP	-----	Intranasal (DPI)	Pulmonary TB	Reduced hepatotoxicity	**[62]**

Pre-clinical Studies for TB Nanoparticles

Recent pre-clinical evidence proves remarkable therapeutic improvements with the use of TB formulations in TB nanoparticles in the animal models. Polymeric nanoparticles that have been loaded with rifampicin have increased 23 log CFU reduction of rifampicin versus free drug in murine infection models. Nanoparticles made up of liposomes and solids lipids exhibit an increase in uptake by the macrophages and extended retention of the drug. In clinical studies, there is prolonged plasma drug concentration of 7-14 days with a one-dose course. Nanoparticle Systems Inhalable The nanoparticle systems have been shown to exhibit enhanced lung deposition and decreased systemic toxicity in study animals [63].

Table 3: List of Pre-clinical studies conducted for the treatment of TB and their details.

Study	Type	Model / Sample	Dose / Route	Safety	Key Outcome	Ref.
β-glucan-chitosan-PLGA NP (RIF)	In-vivo	Mice (n=5-8/group)	Weekly inhalation vs oral RIF	No systemic toxicity	Comparable or better efficacy vs oral RIF	**[64]**
CFZ + Verapamil PLGA NP	In-vitro / In-vivo	Mice (n=12/group), THP-1 cells	Oral (25 + 10 mg/kg)	Reduced toxicity	Improved uptake & sustained release	**[65]**
BDQ Nano-lipid carriers	In-vitro / In-silico	Comparative model	Oral (100 mg eq.)	------	Improved bioavailability & PK profile	**[66]**
RIF SLN formulation	In-vivo	Wistar rats (n=6/group)	Oral (50 mg/kg)	Safe, low toxicity	High drug loading & enhanced bioavailability	**[67]**
D-Cycloserine + Levofloxacin NP	In-vivo	Rats (n=30)	Oral	------	Controlled dual-drug release & improved efficacy	**[68]**
Inhalable dual-drug NP	In-vitro / In-vivo	Murine models + macrophages	Inhalation	Safe, biocompatible	Enhanced lung targeting & CNS penetration	**[69]**
Rifapentine PLGA NP	In-vitro / In-vivo	Mice	Oral (10 mg/kg)	Reduced hepatotoxicity	Sustained release & improved efficacy	**[70]**
INH + MFX PLGA NP	In-vitro	Drug conjugates	50-100 µg/mL	Safe	Dual mechanism, prevents resistance	**[71]**
Liposomal INH + RIF (Bone targeting)	In-vitro / In-vivo	Mice + macrophages	IV (90 days)	Safe	Targeted bone delivery & relapse reduction	**[72]**

Future Prospects

It is hoped that future directions in nanoparticle-based drug delivery systems used in treatment of TB will be improved clinical translation, scale and targeted therapeutic outcomes. The development of ligand-functionalized nanoparticles that are designed to deliver into macrophage specifically with receptors like CD206 and scavenger receptors development are included as advanced strategies. Stimuli-responsive nanoparticles that are able to release the drugs in reaction to pH, redox conditions or enzyme activity in granulomas are being studied to enhance site specific drug delivery. It is expected that nanotechnology will be utilized together with inhalable delivery systems to increase the efficiency of targeting the lungs and nanoparticles that are delivered via dry powder inhalers will have deposition efficiencies that are greater than 50-60% deep lung. The vehicles containing a combination of drugs to treat TB in a single nanoparticle known as co-delivery are currently under investigation with the aim of attaining concomitant pharmacokinetics and decreasing the frequency of the combinatorial dose. New techniques also involve hybrid nanoparticles that are made of polymeric and lipid which have encapsulation efficiencies greater than 85% and better stability. Nanoparticles are being utilized in designing to optimize different formulation parameters and predict a drug release profile using artificial intelligence and machine learning programs. Current studies focus on

making less toxic, biodegradable and meeting regulatory standards of mass production.

Conclusion

Drug delivery systems based on nanoparticles have great potential in treatment of TB due to their increased bioavailability of drugs, increased intracellular delivery and ability of prolonged release of anti-tuberculosis agents. Different nanoparticle preparations such as polymeric, lipid-based and hybrid preparations have proven to have a better pharmacokinetic and pharmacodynamic profile in preclinical research. These systems overcome major shortcomings of traditional therapy including poor drug penetration and systemic poisoning. Regardless of these promising results, there are issues connected with mass production, authorization issues and the safety of the long-term perspective. To develop nanoparticle-based methods in treating TB, further studies that aim at optimizing the formulations, targeted delivery and clinical validation are necessary.

List of Abbreviations

TB: Tuberculosis; MDR-TB: Multidrug-Resistant Tuberculosis; XDR-TB: Extensively Drug-Resistant Tuberculosis; M. tuberculosis: Mycobacterium tuberculosis; NDDS: Novel Drug Delivery System; NP: Nanoparticle; PLGA: Poly (lactic-co-glycolic acid); SLNs: Solid Lipid Nanoparticles; NLCs: Nanostructured Lipid Carriers; PDI: Polydispersity Index; PEG: Polyethylene Glycol; PVA: Polyvinyl Alcohol; TPP: Sodium Tripolyphosphate; MSNP: Mesoporous Silica Nanoparticles; PEI: Polyethyleneimine; HA: Hyaluronic Acid; DPI: Dry Powder Inhaler; BBB: Blood Brain Barrier; CNS: Central Nervous System; CFU: Colony Forming Unit; PK: Pharmacokinetics; EE: Encapsulation Efficiency; TLR: Toll-Like Receptor; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; TNF-α: Tumour Necrosis Factor-alpha; IL-6: Interleukin-6; IFN-γ: Interferon-gamma; IL-10: Interleukin-10; KatG: Catalase-Peroxidase; AMPK: AMP-Activated Protein Kinase; BCG: Bacillus Calmette Guérin; RIF: Rifampicin; INH: Isoniazid; PZA: Pyrazinamide; ETH: Ethambutol; BDQ: Bedaquiline; PA: Pretomanid; MFX: Moxifloxacin; LZD: Linezolid; CFZ: Clofazimine.

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Conflict of Interest

None declared.

Author Contributions

Conceptualization, R.K.M; Methodology, R.K.M.; Software, R.K.M.; Validation, R.K.M.; Formal analysis, S.N.; Investigation, S.H.; Resources, S.H.; Data curation, S.N.; Writing original draft preparation, R.K.M.; Writing review and Editing, R.K.M.; Visualization, R.K.M.; Supervision, J.S & A.K.

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