Use of Nanotechnology to Mitigate Tuberculosis

Tayyaba Akhtar[1]*, Muhammad Ifham Naeem[2], Muhammad Younus[3], Qamar un Nisa[4], Waqas Farooq[5], Hafiz Muhammad Aslam[6], Nida Wazir[7] and Maria Asghar[4]

ABSTRACT

Tuberculosis is a disastrous malady spreading exponentially throughout the world. TB has been long identified as a threat to global health by several international bodies but this threat was amplified upon the identification of multi-drug-resistant germs of TB. Such a scenario arose from several factors regarding TB. Some important factors in this aspect include lack of awareness as TB is prevalent in low-income, low-education countries and exhaustive treatment regimens for TB. Similarly, the adverse effects of drugs are also a factor leading to hampering proper dose implementation. Liver damage caused by anti-TB drugs often leads to a pause in TB medication in turn contributing to increased antibiotic resistance to etiologic agents of TB. Such problems can be easily overcome by developing antibiotic alternatives that can battle antibiotic resistance while reducing the length and adverse effects of the TB medication. Such an option regarding antibiotic alternatives is the use of nanotechnology and nanomaterials. These substances can help us battle anti-microbial resistance by bypassing the defense mechanism of TB bacteria while simultaneously preventing side effects of the drugs through reduced doses.

CITATION

Akhtar T, Naeem MI, Younus M, Nisa Q, Farooq W, Aslam HM, Wazir N and Asghar M, 2023. Use of Nanotechnology to Mitigate Tuberculosis. In: Altaf S, Khan A and Abbas RZ (eds), Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, Vol 4: 679-690. https://doi.org/10.47278/book.zoon/2023.188

CHAPTER HISTORY Received: 25-March-2023 Revised: 12-May-2023 Accepted: 20-June-2023

[1]Department of Epidemiology & Public Health, University of Veterinary and Animal Sciences-Lahore.
[2]KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan.
[3]Department of Pathobiology, KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan.
[4]Department of Pathology, University of Veterinary and Animal Sciences-Lahore.
[5]Institute of Biomedical Sciences, Shanxi University, Taiyuan030006, China.
[6]Department of Biochemistry, University of Agriculture Faisalabad, Pakistan.
[7]Department of Pharmacology and Toxicology, University of Veterinary and Animal Sciences-Lahore.
***Corresponding author:** tayyabaakhtarcheema@gmail.com

1. INTRODUCTION

Tuberculosis is a disastrous malady spreading exponentially throughout the world. TB has been long identified as a threat to global health by several international bodies but this threat was amplified upon the identification of multi-drug-resistant germs of TB. Such a scenario arose from several factors regarding TB. Some important factors in this aspect include lack of awareness as TB is prevalent in low-income, low-education countries and exhaustive treatment regimens for TB. Similarly, the adverse effects of drugs are also a factor leading to hampering proper dose implementation. Liver damage caused by anti-TB drugs often leads to a pause in TB medication in turn contributing to increased antibiotic resistance to etiologic agents of TB. Such problems can be easily overcome by developing antibiotic alternatives that can battle antibiotic resistance while reducing the length and adverse effects of the TB medication. Such an option regarding antibiotic alternatives is the use of nanotechnology and nanomaterials. These substances can help us battle anti-microbial resistance by bypassing the defense mechanism of TB bacteria while simultaneously preventing side effects of the drugs through reduced doses.

2. WHY THE USE OF NANOTECHNOLOGY?

The bacteria *Mycobacterium tuberculosis* (Mtb) is the etiologic agent of tuberculosis (TB) and has dawned on mankind as bad news since antiquity. Despite its long record in past time, TB is still one of the 10 major causes producing death toll in the whole world both developed and under-developed countries included. It is the deadliest infectious disease. It is more serious than other life-threatening illnesses like acquired immune deficiency syndrome and human immunodeficiency virus infection (HIV/AIDS) (WHO 2020). The number of TB cases in 2018 was projected to be 10 million. In the same year, this illness claimed the lives of around 1.5 million people, 251,000 of whom were also HIV-positive. This amount sums up to a staggering number of 4000 fatalities per day (WHO 2020). One of the latest reports from the World Health Organization (WHO) has claimed the existence of infection in 23% of the global population with the latent phase of Mtb. This means that 23% of the global population cannot transmit the infection and are asymptomatic (WHO 2020). TB patients with latent infections however have a chance range starting from 5% up to 15% of developing active TB disease for a lifetime. The rate of infection re-emergence is higher in individuals with immunocompromising diseases such as Human Immuno-Deficiency Virus infection, undernutrition, and diabetes (Getahun et al. 2015). This is the reason for the higher incidence rates of TB in areas where many of these conditions are prevalent among the population. Among these regions are Africa and Southeast Asia, which together account for 68% of newly diagnosed cases of tuberculosis (WHO 2020). For drug-sensitive TB, a 2-month regimen of isoniazid (INH), ethambutol (ETB), pyrazinamide (PZA), and rifampicin (RIF) is now advised. After completing this course, a 4-month RIF plus INH phase should be implemented (Nahid et al. 2016; WHO 2018). WHO's 194 Member States routinely report drug-sensitive tuberculosis cases to it with cureability rates of at least 85% (WHO 2020). The major reason for a combined drug prescription of anti-TB drugs is to minimize the chances of drug-resistance development in Mtb strains, by attacking them with different modes of action all at once. However, the growth of drug-resistant TB strains has been caused by the inconsistent medication supply, patients' noncompliance with the treatment protocol, and the wrong execution of drug intake regimens due to a lack of competent monitoring (Aziz et al. 2004). Multidrug-resistant (MDR) strains are Mtb bacteria that are resistant to the preferred medications, RIF and INH. Conversely, MDR Mtb bacteria that contain an extra resistance to a fluoroquinolone medication (such as levofloxacin or moxifloxacin) in addition to a second-line injectable medication (like kanamycin, amikacin (AMK), or capreomycin) are referred to as extensively drug-resistant (XDR) strains. Additionally, during the past several years, numerous reports of cases involving all first- and second-line drug-resistant strains of tuberculosis have surfaced (Dheda et al. 2014).

3. PATHOGENESIS

Being an obligate intracellular pathogen, Mtb has unique human reservoirs. Mtb infection is initiated by the touch down of its bacilli in the lungs after inhalation of contaminated droplets expired by an individual affected with the active form of pulmonary TB (droplets can have expelled by inhalation at a great speed as in case when a patient coughs or sneezes). Once the bacilli reach the space of alveoli, they become internalized by the phagocytosis of alveolar macrophages (AMs). The innate immune system's primary action cells are alveolar macrophages. Pathogen-associated molecular patterns, or PAMPs, are recognized by the host cell's PPRs, or pattern recognition receptors. PAMPs are typically seen on the bacilli's outermost membrane during invasion (Figure 1). PAMPs cause the release of cytokines and chemokines, which in turn causes other phagocytic cell types, such as neutrophils, dendritic cells, and interstitial macrophages, to assault the infection site (Akira et al. 2006; Philips and Ernst 2012). In several cases ranging from 20 to 25% of the cases, macrophages can thoroughly quarantine the infection by eliminating the invading agent through phagocytosis (Verrall et al. 2014). However, the majority of invading Mtb bacilli manage to escape elimination by immunity cells (Gengenbacher and Kaufmann 2012). The Mtb saves itself by residing in the phagosome cells by the mechanism of the ESX1 secretion activation system. This system releases several other molecules along with proteins that target the internal systems of the phagosome. These attacks disrupt the membrane of the phagosome subsequently leading to the release of mycobacterial components. These components are released into the cytosol of the macrophage.

These molecules and proteins enable Mtb to arrest the maturation of the phagosome by hindering the fusion of lysosomes. Then Mtb moves on to transform the highly hostile environment inside a phagosome into a somewhat milder and survivable condition for itself. This enables it to replicate to replicate inside the macrophage once it survives through harsh conditions (Pai et al. 2016; Cheung et al. 2019). As the infected phagosome cells migrate to the lymph nodes of the pulmonary system they are processed and presented with antigens for priming of T cell priming (both CD4+ and CD8+). The T cells are produced by the adaptive immune response system, 15–18 days post-Mtb infection. These T cells then migrate to the site of the Mtb infection guided by the chemokines produced by infected cells (Zuñiga et al. 2012). Consequently, the pathogen can:

- Face elimination by the immune response cells of the host
- It may progress to active disease conditions (this situation mainly pops up in immunocompromised hosts)
- It may sustain itself in specific structures called granulomas– the typical pathological sign of tuberculosis (Pai et al. 2016).

4. CHALLENGES IN THE TREATMENT OF TUBERCULOSIS

Collectively, the occurrence of TB infection happens as a dynamic process comprising several pathological phases of granulomas coexisting (solid, caseous, and cavitary granuloma) simultaneously. This forces the bacilli to adapt to an ever-changing array of microenvironments for the sake of survival. The sub-optimal drug concentration levels achieved in the caseum of necrotic granuloma along with the resistance capabilities of dormant bacteria against anti-TB drugs make their eradication challenging. Resultantly, the non-replicating bacteria, which may seem harmless due to the asymptomatic nature of the infection, serve as TB re-activation reservoirs and drug-resistance gene pools. Additionally, a situation like an LTBI may emerge after a drug-based treatment of active infection disease. Such circumstances may arise if the bacteria are not fully eradicated during the treatment. The remaining few that are still present in the body can maintain themselves in a latent phase which later leads to relapse of the disease after a certain amount of time has passed (Behinaein and Cirillo 2019; WHO 2020). These contributing factors also help us to

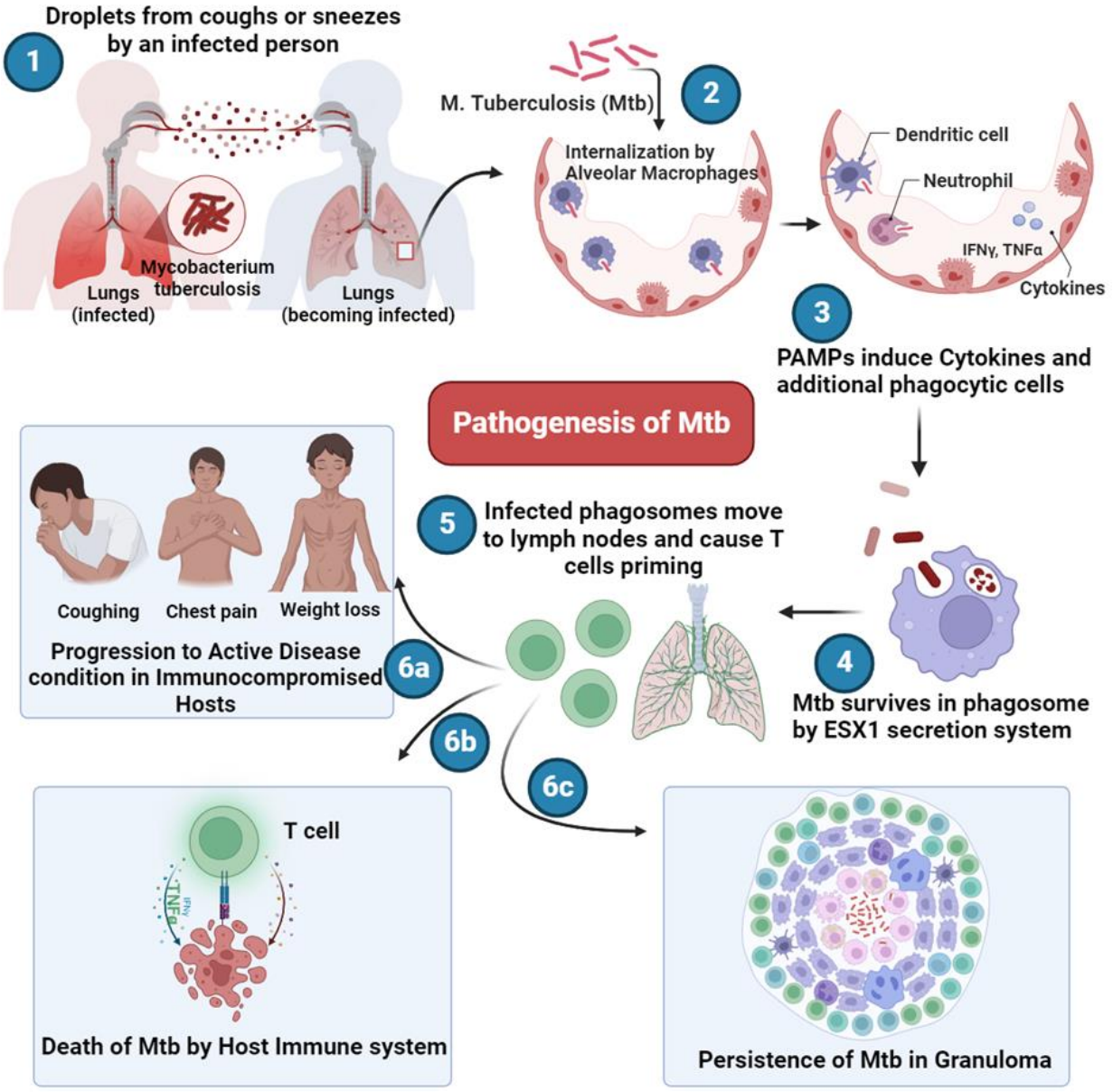

Fig. 1: Pathogenesis of *M. tuberculosis* infection.

comprehend the long duration of TB treatments mandatory for curing active TB infections. This much time is implemented for anti-TB drug administration to eradicate the infectious agent thoroughly. The drugs have high priority and more time to target the bacteria in the granulomas inside host cells.

TB or Tuberculosis has been a major killer disease around the globe. Even its treatment is arduous as it requires several first-line anti-TB drugs to be administered regularly for at least 6 months to get rid of the disease. Still, this is a tricky and arduous move to try and control TB with the administration of antimycobacterial drugs for several reasons including:

- Treatment through chemotherapy requires drug administration for a long duration,
- The effectiveness of the antimycobacterial drugs to reach targets and produce antimycobacterial effects upon them is sub-par

- The effectiveness of TB drugs is reduced due to various reasons such as poor stability and permeability
- All antimycobacterial agents are usually toxic to normal body cells too
- A large number of TB patients show non-compliance to prescribed medication protocol this factor can have attributed to the fact that TB therapy is very lengthy and has severe life-altering side effects.

Liver damage and hepatotoxicity are highly common and sometimes deadly adverse effects seen when these anti-TB medicines are used. Doses have an impact on these side effects. In addition, using INH also results in neurotoxicity. When EMB is used, eye toxicity results. In a similar way, STR results in permanent nephrotoxicity and ototoxicity even if it does not harm the liver. Since most of these issues are related to insufficient drug administration techniques, drug delivery technology and the scientific community, particularly formulation scientists, face significant challenges (Du Toit et al. 2006).

5. USE OF NANODELIVERY SYSTEMS

The use of nanocarriers-based drug delivery systems is an innovative and modern strategy denoting the future of medicine in the war against several types of diseases. The major advantages of drug delivery systems based on nanocarriers over free drugs are improved drug bioavailability and controlled drug release with desired dosage over a timeline according to the need of the treatment regimen. It also protects the drug agent by preventing it from inactivating through the entrapment of the chemical agent. The controlled drug release system keeps the drug dose maintained at the desired level. This reduces the number of doses administered to the patient. Reduced doses in turn minimize the adverse effects of the drug administration and intake frequency (Costa-Gouveia et al. 2017). For effectively targeting *M. tuberculosis* reservoirs, nanocarriers of various several types have been developed. Some of the many common examples of nanocarriers include liposomes, polymeric nanoparticles, nanocapsules, solid lipid nanoparticles, micelles, nanogels, inorganic nanocarriers, dendrimers etc. There are various methods of integrating chemotherapeutic agents into nanocarrier systems. Some common examples of these integration methods include but are not limited to adsorption, physical encapsulation, chemical conjugation etc. The most significant aspect regarding the utilization of nanocarrier systems is their potential ability to finely target the host cells either through passive accumulation or active targeting (Costa-Gouveia et al. 2017; Ladavière and Gref 2015).

6. IMPORTANT FACTORS TO BE CONSIDERED FOR USING NANO-DELIVERY

To produce maximum therapeutic benefits from a drug it must be made carefully. This extreme care system implemented in drug formulation practices forms the core concept behind an efficient drug delivery system (Fig. 2). The four "D's" stand for the four qualities that a drug delivery system should possess. These consist of disease, drug, delivery, and destination. The disease is the sole changeable factor among these four (Jiang et al. 2007). When the pace, location, or both of a medication release are altered, a modified-release system is created. Most often, encapsulation methods are utilized to create customized release systems. This is a widely used technique for creating controlled drug release systems that are heavily utilized in the pharmaceutical sector.

While other non-polymeric drug carriers, such as lipids, can also be utilized in the form of solid lipid nanoparticles (SLNs), chitosan, alginic acid, and poly(lactide-co-glycolide) (PLG) are among the polymers that have been shown to provide good results. Researchers from all over the world are becoming more interested in liposomes because of their promising applications in the field of medication delivery systems. Unrelated to the carrier system, a drug delivery system's main objective is improving the drug's bioavailability. Increased drug bioavailability can be achieved by bypassing the potential factors that can influence it hindering its maximum effectiveness. Various nano-particle approaches have been formulated

and presented to the world for improvement in delivering chemotherapeutic drugs to their exclusive target sites. By aggressively localizing the chemotherapeutic agent's chemical and pharmacological action on the intended location or organ, this strategy serves to increase the therapeutic index value of the drug. This method also reduces the unfavorable side effects of the medications and non-target assaults. Therefore, it can be concluded that drug delivery systems based on nanoparticulates can also contribute in increasing tolerance to toxic chemotherapy by lowering the lethal index value of the medication while concurrently increasing its bioavailability (Shegokar et al. 2011). It can be noted from the current knowledge that the application of nanocarrier systems for anti-TB drugs is suspected to produce various benefits for TB patients including, thorough treatment through utilization of smaller doses, it will be further complemented by the overwhelming response of first-pass metabolism, bypassing the gastrointestinal tract and the large number of efflux systems associated with it and dodging the pH-dependent or enzymatic degradation.

7. TYPES OF NANO-DELIVERY SYSTEMS

Polymeric nanoparticles or NPs are drug carrier systems. They are included in the nanoparticles category as they have a diameter of less than 1 m. The nanoparticle agents like nanospheres (NSs) and nanocapsules (NCs) differ according to their structural and compositional organization (28). Nanoparticles consist of a wide variety of polymeric shells encompassed by an oily core. The desired drug may be dissolved in this core of the nanoparticle agent. Another option is the adsorption of the drug to the polymeric wall. In contrast to this system, there is another formulation for nanoparticles that do not have oil in their ingredients. They are formed by a polymeric drug-entrapping matrix that entraps or adsorbs the drugs (Vauthler-Holtzscherer et al. 1991; Allémann et al. 1993; Puisieux et al. 1994; Bhardwaj et al. 2005; Jones et al. 2008). These nanoparticle systems have been developed by scientists for several types of therapeutic applications in the pharmaceutical industry. The main applications of these systems include the delivery of drugs administered through parenteral, ophthalmic or oral administration (Brasseur et al. 1991; Puisieux et al. 1994; Couvreur et al. 1995; Yoo et al. 2000). Nanoparticles can improve the solubility of comprising agents. Nanoparticles also reduce the therapeutic dose of a drug by improving its absorption of active ingredients. Additionally, the nanoparticles have several advantages when administered in the blood vessels as they lack thrombogenic properties, inert, non-toxic, non-inflammatory (they do not activate neutrophils), and non-immunogenic, all while avoiding the invasion of the reticuloendothelial system of vessels. Occasionally, PNs are used to reach target tissues or work at the surface of the cell (Schaffazick et al. 2003; Alexis et al. 2008; Saraf 2010; Kumari et al. 2010) of information gained by the characterization of these parameters can direct the proposition of models depicting the organization of the nanoparticles on a molecular level, which will be dependent on the qualitative and quantitative composition of the formulations. Moxifloxacin (MX), an antibiotic belonging to the fluoroquinolone class of drugs, has been discovered to be effective against *M. tuberculosis* with its potential reach close to RIF (Gosling et al. 2003). Yet, its intracellular activity against *M. tuberculosis* in macrophages is low. MX-poly (butyl cyanoacrylate) (PBCA) nanoparticles were created by (Kisich et al. 2007) to enhance the efficacy of MX against intracellular M. tuberculosis in macrophages. Moxifloxacin (MX-NP)-loaded PBCA nanoparticles were created by anionically polymerizing n-butyl-2-cyanoacrylate in the presence of a chemical agent. By measuring the particle size and polydispersity of the size distribution, MX-NP was successfully characterized. Compared to pharmacological agents without encapsulation, MX that had been encapsulated quickly and roughly three times more efficiently digested in macrophages. It was discovered to stay in the extracellular matrix of the macrophages for six times longer than the free drug did. When M. tuberculosis was positioned intracellularly, encapsulated MX was able to limit development at a concentration of 0.1 gmL−1, whereas free MX required a concentration of 1 gmL−1 to provide the same result. The process of encapsulating MX in PBCA nanoparticles improved its intake and half in the macrophages and resulted in an elevated drug

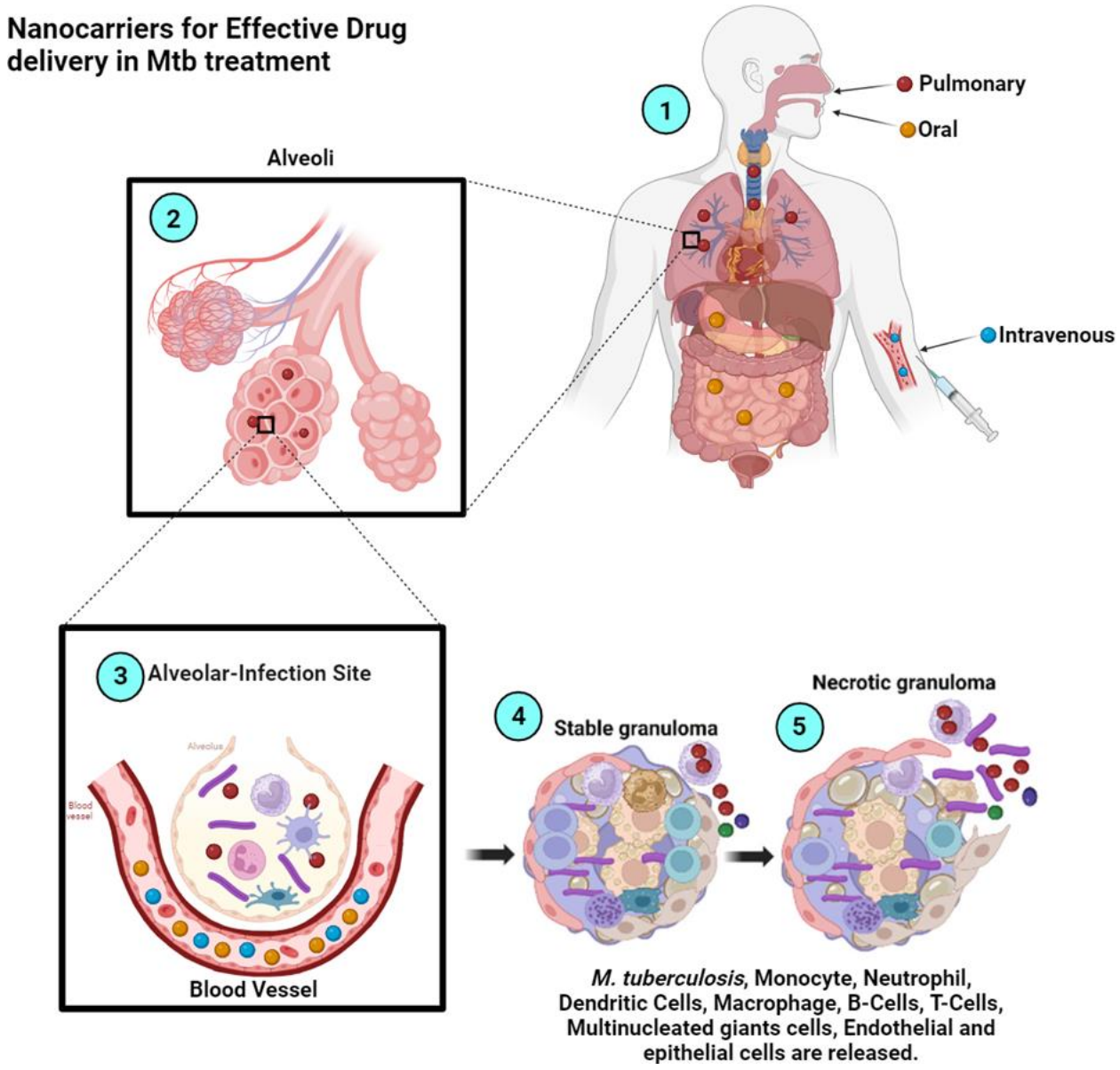

Fig. 2: Nanocarriers for drug delivery in Mtb via different routes of administration.

efficacy against tuberculosis inhabiting macrophages. A variety of techniques have been proposed in the literature for the preparation of polymer nanoparticles (PNs). These can be broadly categorized into methods based on the polymerization of dispersed monomers (alkyl cyanoacrylate) in situ (Gallardo et al. 1993; Chouinard et al. 1994; Lenaerts et al. 1995; Sakuma et al. 1997; Lambert et al. 2000) or the precipitation of preformed polymers (Guterres et al. 1995a; Espuelas et al. 1997; Quintanar-Guerrero et al. 1998; Marchais et al. 1998; Quintanar-Guerrero et al. 1998; Santos-Magalhães et al. 2000). These include poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(-caprolactone) (PCL), methacrylic acid copolymers, and acrylic or methacrylic ester. Irrespective of the method used to prepare, the products are formed as colloidal suspensions in aqueous phase. Nevertheless, the storage time can cause the aggregation of the nanoparticles in the middle of the

suspension, bringing about the formation of precipitates (Molpeceres et al. 1997; Schaffazick et al. 2002) In addition, problems with the chemical stability of polymer and raw materials including drugs, are likely to occur (Guterres et al. 1995b; de Chasteigner et al. 1996; Saez et al. 2000). The mentioned problems can be reduced by employing drying processes, such as freeze drying or sublimation, that allow dehydration while averting particle degradation (Franks 1998; Schmidt and Bodmeier 1999). based on colloidal nature, technical difficulties are dealt with in the physicochemical characterization of NPs. The characterization of the suspensions involves a morphological evaluation, a determination of particle size, an analysis of the molar mass distribution of the polymer, the determination of zeta potential, a measurement of the pH, the determination of the amount of drug affiliated with nanostructures, examination of the drug release kinetics and measurement of stability over some time (Schaffazick et al. 2003).

8. NANO-STRUCTURED LIPID CARRIERS AND SOLID LIPID NANOPARTICLES

Solid Lipid Nanoparticles or SLNs are manufactured from lipids that are stabilized by surfactants and become solid at room temperature as well as body temperature. The waxes, triglycerides, or a mixture of glycerides are the types of lipids utilized for the manufacturing of SLNs. The utilization of the very same types of lipids produces perfect crystals with high organization, which decreases the encapsulation efficiency, which ranges from 25–50% for these systems. Moreover, during storage, the drug may be expelled from the particle after the polymorphic transition from the form to the form, which is more stable. Therefore, to enhance the efficiency of the encapsulation and reduce the expulsion of drugs during its storage in the nanoparticles. NLCs of three different types have arisen from the basic structures. The first model of NLCs is known as “imperfect NLCs”. It comprises a combination of various glycerides made up of variable types of fatty acids. The combination methodology increases the distance among the fatty acid glyceride chains producing imperfections in the crystals. These imperfections produce more open space among the chains to fit in more drugs. These increased spaces in turn increase the encapsulation efficiency of the NLCs. The other model called for NLC formulation is “amorphous NLCs”. It is a combination of lipid liquids with lipid solids. An example of such lipids is Miglyol (triglyceride, caprylic/capric); when large amounts of liquid lipids are mixed with solid lipids it leads to the production of particles in an amorphously solid state. This prevents the expulsion of the drug during storage since the process of lipid crystallization does not occur under these conditions. The third model is called “multiple NLCs;” this is a dispersive immersion of liquid lipids in solid lipids along with water. In this type of NLC, the liquid lipid molecules mix the lipid solid with exceeding solubility producing a separation of phases and the appearance of liquid lipid nanocages into the matrix of solid lipids where the drug is encapsulated (Souto et al. 2007). A major advantage of SLN is its superb chemical and physical inertness, making it a suitable partner for the protection of the labile drugs from falling victim to degradation. It also grants drugs with the ability to be introduced into the body through various routes, such as oral, parenteral and cutaneous due to their minute size and enhanced biocompatibility (Souto et al. 2011). Another advantage of these systems is the controlled drug and the ability of the SLNs to make water-insoluble drugs soluble in this solvent, enhancing drug absorption (Mehnert and Mäder 2012; Taveira et al. 2012; Potta et al. 2010). SLNs and NLCs may be produced by melt emulsification or using ultrasound, mechanical mixing, high-pressure homogenization, emulsification-evaporation of the solvent, or microemulsions. The emulsification solvent evaporation yields particles with smaller sizes due to the lower viscosity of the internal phase since the lipid is dissolved in an organic solvent rather than being melted. This method has the advantage of avoiding exposure to the active compound at elevated temperatures but shows the disadvantage associated with the use of organic solvents (Souto et al. 2011).

9. FUTURE PERSPECTIVES OF NANOTECHNOLOGY

Nanotechnology is a powerful weapon in the battle against drug-resistant TB. Additionally, the combination of nanocarrier-based systems of drug delivery with the pulmonary administration methodology provides physicians with one of the most encouraging approaches to treating TB thoroughly. The use of pulmonary delivery in medication administration systems creates a non-invasive way to consume drugs. This application, especially with systemic action medication intake, has a promising future (Rani et al. 2018). When combined with the pulmonary administration technique, a significant component of the development of a nanomedicine-based strategy with long-term potential can be utilized as a critical component for tuberculosis control, particularly in developing nations. These are the areas without adequate healthcare systems for the majority of its residents (Salamanca-Buentello et al. 2005). The patient itself can use the nanoparticle medications administered with an inhaler device. This increases its use and accessibility for TB patients as a tool for anti-TB treatment. This minimizes the bulk of the expenses associated with treating tuberculosis by lowering the requirement for specialized medical equipment and staff, despite the increase in the number of research reports being published to present the advantages of drug administration through the respiratory route. However, the lack of uniform and effective techniques for administering drugs in pre-clinical trials generally leads to the production of poor results and ultimately translates the methodology as a low-success project. Passive inhalation of the chemical agent is required for the fundamental usage of inhalation devices for delivery through the respiratory route. Variations in lung capacity and inhalation lead to differences in the amount of medication administered. On the other hand, a precise assessment of the amount going into the lungs is required. This is a critical aspect since ineffective medication delivery can lower its effectiveness due to drug loss in the storage container, aerosol drug-generating device tubes, delivery device attachments, and the animal's nasopharyngeal region. These losses are often mistaken for the ineffectiveness of the medications being used to treat tuberculosis. Due to inadequate dosage, it can be a risk factor for the emergence of drug resistance. Due to such issues, researchers prefer invasive techniques to deliver drugs to the respiratory system. These techniques include intratracheal intubation to achieve better and more accurate delivery of the dose of the drugs in the lungs. This is why most preclinical models are markedly different from inhalation methodologies used in humans making the results from experiments and trials a bit unsure for the field application (Kunda et al. 2018).

10. CONCLUSION

Rapid transmission of TB in the human population was already a threat to global health that was amplified by the emergence of antibiotic resistance among *Mycobacteria*. This is a matter of grave concern as it means that all previous medications will fail to battle TB and assist in its treatment. This dire threat This situation called for the development of an alternative method to overcome bacterial resistance and increase the effectiveness of anti-TB drugs. Such an alternative was identified to be nanotechnology. Nanoparticles can be used to bypass antibiotic resistance mechanisms of the bacteria increasing the bioavailability of the drug. On the other hand, the nanopolymers and other nanotechnology-based carrier systems can be used to adjust the dosing regimen of antibiotics to make the treatment less exhaustive for the patient while lowering its toxic effects at the same time. Researchers have been working tirelessly to formulate more effective and less toxic nanoparticles that can be manufactured economically and safely for mass production. This will enable the coating of all drugs in nanomaterials leading to an increased efficiency of the medicine as an overall effect.

REFERENCES

Akira S et al., 2006. Pathogen recognition and innate immunity. Cell 124: 783-801.

Alexis F et al., 2008. Factors affecting the clearance and biodistribution of polymeric nanoparticles. Molecular Pharmaceutics 5(4): 505-515.

Allémann E et al., 1993. Drug-loaded nanoparticles: preparation methods and drug targeting issues. European Journal of Pharmaceutics and Biopharmaceutics 39(5):173-191.

Aziz A et al., 2004. Anti-Tuberculosis Drug Resistance in the World: Third Global Report: The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance 1999-2002, WHO, Geneva, Switzerland.

Behinaein P and Cirillo JD, 2019. Tuberculosis Host-Pathogen Interactions (Eds: Cirillo J and Kong Y). Springer Nature, Switzerland 2019: 2342.

Bhardwaj V et al., 2005. Pharmaceutical aspects of polymeric nanoparticles for oral drug delivery. Journal of Biomedical Nanotechnology 1(3): 235-258.

Brasseur N et al., 1991. Adsorption of hematoporphyrin onto polyalkylcyanoacrylate nanoparticles: carrier capacity and drug release. International Journal of Pharmaceutics 70(1-2): 129-135.

Cheung LS et al., 2019. in Tuberculosis Host-Pathogen Interactions (Eds: J. Cirillo, Y. Kong), Springer Nature, Switzerland 2019: 63–93.

Chouinard F et al., 1994. Poly (alkylcyanoacrylate) nanocapsules: physicochemical characterization and mechanism of formation. Pharmaceutical Research 11: 869-874.

Costa-Gouveia J et al., 2017. How can nanoparticles contribute to antituberculosis therapy?. Drug Discovery Today 22(3): 600-607.

Couvreur P et al., 1995. Controlled drug delivery with nanoparticles: current possibilities and future trends. European Journal of Pharmaceutics and Biopharmaceutics 41(1): 2-13.

de Chasteigner S et al., 1996. Freeze-drying of itraconazole-loaded nanosphere suspensions: a feasibility study. Drug development research, 38(2): 116-124.

Dheda KT et al., 2014. Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis. Lancet Respiratory Medicine 2(4): 321-338.

Du Toit LC et al., 2006. Tuberculosis chemotherapy: current drug delivery approaches. Respiratory Research 7(6): 1-18.

Espuelas et al., 1997. Poly (ε-caprolacton) nanospheres as an alternative way to reduce amphotericin B toxicity. International Journal of Pharmaceutics 158(1): 19-27.

Franks F, 1998. Freeze-drying of bioproducts: putting principles into practice. European Journal of Pharmaceutics and Biopharmaceutics 45(3): 221-229.

Gallardo M et al., 1993. Study of the mechanisms of formation of nanoparticles and nanocapsules of polyisobutyl-2-cyanoacrylate. International Journal of Pharmaceutics 100(1-3): 55-64.

Gengenbacher M and Kaufmann SHE, 2012. Mycobacterium tuberculosis: success through dormancy. FEMS Microbiology Review 36(3): 514-532.

Getahun H et al., 2015. Latent Mycobacterium tuberculosis Infection. New England Journal of Medicine 372(22): 2127-2135.

Gosling RD et al., 2003. The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis. American Journal of Respiratory and Critical Care Medicine 168(11): 1342-1345.

Guterres SS et al., 1995a. Poly (D, L-lactide) nanocapsules containing non-steroidal anti-inflammatory drugs: gastrointestinal tolerance following intravenous and oral administration. Pharmaceutical Research 12: 1545-1547.

Guterres SS et al., 1995b. Poly (DL-lactide) nanocapsules containing diclofenac: I. Formulation and stability study. International Journal of Pharmaceutics 113(1): 57-63.

Jiang W et al., 2007. Advances and challenges of nanotechnology-based drug delivery systems. Expert Opinion on Drug Delivery 4(7): 621–633.

Jones SA et al., 2008. Preparation and characterisation of polymeric nanoparticles using low molecular weight poly (vinyl alcohol). Journal of Biomedical Nanotechnology 4(3): 319-325.

Kisich KO et al., 2007. Encapsulation of moxifloxacin within poly (butyl cyanoacrylate) nanoparticles enhances efficacy against intracellular Mycobacterium tuberculosis. International Journal of Pharmaceutics 345(1-2): 154-162.

Kumari A et al., 2010. Biodegradable polymeric nanoparticles based drug delivery systems. Colloids and Surfaces B: Biointerfaces 75(1): 1-18.

Kunda NK et al., 2018. Respiratory tract deposition and distribution pattern of microparticles in mice using different pulmonary delivery techniques. Vaccines 6(3): 41.

Ladavière C and Gref R, 2015. Toward an optimized treatment of intracellular bacterial infections: input of nanoparticulate drug delivery systems. Nanomedicine 10: 3033-3055.

Lambert G et al., 2000. Polyisobutylcyanoacrylate nanocapsules containing an aqueous core as a novel colloidal carrier for the delivery of oligonucleotides. Pharmaceutical Research 17: 707-714.

Lenaerts V et al., 1995. Nanocapsules with a reduced liver uptake: targeting of phthalocyanines to EMT-6 mouse mammary tumour in vivo. European Journal of Pharmaceutics and Biopharmaceutics 41(1): 38-43.

Marchais H et al., 1998. Entrapment efficiency and initial release of phenylbutazone from nanocapsules prepared from different polyesters. Drug Development and Industrial Pharmacy 24(9): 883-888.

Mehnert W and Mäder K, 2012. Solid lipid nanoparticles: production, characterization and applications. Advanced Drug Delivery Reviews 64: 83-101.

Molpeceres J et al., 1997. Stability of cyclosporine-loaded poly-X-caprolactone nanoparticles. Journal of Microencapsulation 14(6): 777-787.

Nahid P et al., 2016. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases 63: e147- e195.

Pai M et al., 2016. Tuberculosis: the story after the Primer. Nature Reviews Disease Primers 6(29): 1-2.

Philips JA and Ernst JD, 2012. Tuberculosis pathogenesis and immunity. Annual Review Pathology: Mechanism of Diseases 7: 353-384

Potta SG et al., 2010. Development of solid lipid nanoparticles for enhanced solubility of poorly soluble drugs. Journal of Biomedical Nanotechnology 6(6): 634-640.

Puisieux F et al., 1994. Polymeric Biomaterials, edited by S. Dimitriu, Marcel Dekker, New York, United States.

Quintanar-Guerrero D et al., 1997. A mechanistic study of the formation of polymer nanoparticles by the emulsification-diffusion technique. Colloid and Polymer Science 275: 640-647.

Quintanar-Guerrero D et al., 1998. Preparation techniques and mechanisms of formation of biodegradable nanoparticles from preformed polymers. Drug Development and Industrial Pharmacy 24(12): 1113-1128.

Rani S et al., 2018. Smartly engineered PEGylated di-block nanopolymeric micelles: duo delivery of isoniazid and rifampicin against Mycobacterium tuberculosis. AAPS PharmSciTech 19: 3237-3248.

Saez A et al., 2000. Freeze-drying of polycaprolactone and poly (D, L-lactic-glycolic) nanoparticles induce minor particle size changes affecting the oral pharmacokinetics of loaded drugs. European Journal of Pharmaceutics and Biopharmaceutics 50(3): 379-387.

Sakuma S et al., 1997. Oral peptide delivery using nanoparticles composed of novel graft copolymers having hydrophobic backbone and hydrophilic branches. International Journal of Pharmaceutics 149: 93-106.

Salamanca-Buentello F et al., 2005. Nanotechnology and the developing world. PLoS Medicine 2(5): 97.

Santos-Magalhães NS et al., 2000. Colloidal carriers for benzathine penicillin G: nanoemulsions and nanocapsules. International Journal of Pharmaceutics 208(1-2): 71-80.

Saraf S, 2010. Applications of novel drug delivery system for herbal formulations. Fitoterapia 81(7): 680-689.

Schaffazick SR et al., 2002. Caracterização e estudo de estabilidade de suspensões de nanocápsulas e de nanoesferas poliméricas contendo diclofenaco. Acta Farm. Bonaerense 21(2): 99-106.

Schaffazick SR et al., 2003. Caracterização e estabilidade físico-química de sistemas poliméricos nanoparticulados para administração de fármacos. Química Nova 26: 726-737.

Schmidt C and Bodmeier R, 1999. Incorporation of polymeric nanoparticles into solid dosage forms. Journal of Controlled Release 57(2): 115-125.

Shegokar R et al., 2011. Present status of nanoparticle research for treatment of tuberculosis. Journal of Pharmacy and Pharmaceutical Sciences 14(11): 100–116.

Souto EB et al., 2007. Lipid nanoparticles (SLN®, NLC®) for cutaneous drug delivery: structure, protection and skin effects. Journal of Biomedical Nanotechnology 3(4): 317-331.

Souto EB et al., 2011. Nanopartículas de lipídios sólidos: métodos clássicos de produção laboratorial. Química Nova 34: 1762-1769.

Taveira SF et al., 2012. Development of cationic solid lipid nanoparticles with factorial design-based studies for topical administration of doxorubicin. Journal of Biomedical Nanotechnology 8(2): 219-228.

Vauthler-Holtzscherer C et al., 1991. Methodology for the preparation of ultra-dispersed polymer systems. STP Pharma Sciences 1(2): 109-116.

Verrall AJ et al., 2014. Early clearance of Mycobacterium tuberculosis: a new frontier in prevention. Immunology 141(4): 506-513.

WHO, 2018. WHO Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care: Essential First-Line Antituberculosis Drugs, WHO, Geneva, Switzerland.

WHO, 2020. WHO | Global Tuberculosis Report 2019, WHO, Geneva, Switzerland.

Yoo HS et al., 2000. Park, In vitro and in vivo anti-tumor activities of nanoparticles based on doxrubicin—PLGA conjugates. Journal of Controlled Release 68: 419.

Zuñiga J et al., 2012. Cellular and Humoral Mechanisms Involved in the Control of Tuberculosis. Clinical and Developmental Immunology 2012: 193923.