1. Introduction

Tuberculosis (TB) is still far from being a health concern of the past. Although less frequent in Europe and North America, it has a strong prevalence in Africa, Asia and South America. In 2014, this resulted in 1.5 million deaths, making it the leading cause of death in the world from infectious diseases (Mathers, et al., 2009). Diseases continue to be a threat and pose many obstacles in the development of mankind. For some, there is permanent cure but for others the cure is temporary with continuous advancement in science and technology and constant research. Ways are evolving out for the treatment of diseases otherwise considered as incurable. Yet another strike of this constant Endeavor is towards the betterment of existing therapy in terms of enhancement of efficiency of treatment, cutting short the duration of therapy and curtailing the side effect of drug (Penney, 1990).

TB is caused by the infection of Mycobacterium tuberculosis (MTB). It can affect practically all organs of the human body, but the lung is of particular high incidence, being designed as pulmonary TB. This is expected since the infection starts with the inhalation of infectious aerosol particles released from close contacts, leading the bacteria directly to the lung (Costa, et al., 2016). Due to their size, the bacilli are able to reach the pulmonary alveoli, where they are phagocytized by the alveolar macrophages. Inside the alveolar macrophages, the bacilli resist to the bactericidal mechanisms of the macrophage by preventing phagosome lysosome fusion (phagolysosome) (Guidi-Rontani, et al., 1999).

Therefore, they can multiply and eventually escape from the lung through the blood stream and lymphatic system, spreading to other organs of the body, resulting in extra pulmonary TB. It is estimated that one-third of the world's population is latently infected with MTB. Latent individuals do not transmit the disease to others and latent infection can only progress to an active form of disease in 5%–10% of the cases (Young, et al., 2009). However, there are some conditions that are associated with high risk of susceptibility to MTB infection, namely HIV, diabetes, long-term use of corticosteroids, TNF-α blockers, polymorphisms in vitamin D receptors or in IL-12 and IFN-γ genes, malnutrition and smoking. Recently, WHO proposed the eradication of Tuberculosis until 2050 and although possible, constitutes an ambitious goal to approach, requiring more effective technologies (Stover, et al., 2014).

TB current therapy and limitations Currently available chemotherapy includes first-line drugs, such as isoniazid (INH), pyrazinamide (PZA), rifampicin (RIF) and ethambutol (EMB); second-line drugs, such as injectable agents (streptomycin, kanamycin, amikacin,

capreomycin and viomycin), fluoroquinolones (ofloxacin, levofloxacin, gatifloxacin and moxifloxacin) and other oral agents (ethionamide, prothionamide, cycloserine, terizidone and para-amino salicylic acid) (Du Toit, et al., 2006; Guy, et al., 2008). According to the WHO guidelines, the standard regimen for TB treatment includes daily administration of INH, RIF, PZA and EMB for 2 months, followed by daily administration of INH and RIF for further 4 months. The second-line drugs are used when treatment with first-line drugs fails or in presence of multidrug-resistant TB cases (MDR-TB). These drugs are less effective, more toxic, and unavailable in many countries due to high costs. Up to December of 2012, the most recent drugs dated back 50 years. Some prominant rsearchers emphasized how essential further research in new drug target is needed in order to fight drug resistant TB (Filler, et al., 2009; Pruden, 2013). There are several new drug candidates currently in research and in clinical trials, and recently two new drugs (bedaquiline and delamanid) have been approved for the treatment of MDR-TB, when other alternatives are not available. Bedaquiline was approved by the Food and Drug Administration (FDA) in December 2012 and has completed phase II trials. However, in order to optimize treatment regimens, phase III trials and phase IV studies are needed. Delamanid was approved by the European Medicine Agency (EMA) in April 2014 and is currently being tested in a phase III clinical trial for the treatment of MDR-TB in adults and in children (Nelson, et al., 2004; Schaaf, et al., 2002). Also, several existing drugs are in a state of reevaluation. The current treatment is usually associated with severe adverse effects, resulting in poor compliance, which is one of the main reasons for the appearance of multidrug resistant strains and treatment's failure. Moreover, the current therapies have a limited ability to penetrate granulomas and have reduced effects on dormant bacilli. In this context, improved treatments are needed to shorten TB treatment duration, prevent resistance and reduce lung injury. Besides the above-mentioned limitations, the administration routes have also critical challenges. The oral route is the most convenient and least expensive; however, prolonged administration of high doses is needed and sub-therapeutic levels of anti-TB drugs reach the site of infection,due to the sloweronset of action, the hepatic first-passmetabolism and harsh gastro-intestinal absorption (Pham, et al., 2015). The oral route is also associated with severe side effects as a result of high systemic exposure. Compared to the oral route, the parenteral and pulmonary routes have highest bioavailability and are not subject to first-pass metabolism. Nevertheless, parenteral

administration is a painful route of administration and requires the presence of healthcare workers (Zech, et al., 1995).

The tuberculosis bacteria are always present in the body which cannot be spread further due to the presence of our active immune system in the body which helps to defence with the infection and prevent to move turning into active Tuberculosis. It the case of latent tuberculosis, which could become active (Mack, et al., 2009). Active tuberculosis means the bacteria (M. Tuberculin) growing and showing, symptoms of tuberculosis. If active tuberculosis found in human lungs, it would easy to spread chance of infection in another part of the body.

The effective chemotherapy of TB began in 1944 when streptomycin (SM) was regulated to the principal tolerant. The ensuing utilization of the first and second-line of tuberculosis drugs prompt a lofty decrease in TB occurrence. None the less, the non-attendance of novel powerful TB treatment remains a note worthy general well being danger worldwide because of quick improvement of multi-drug resistant strains (MDR) and extremely drug resistant strains (XDR). Advancement of intense chemotherapeutic choices is vital to averting future epidemic of this insidious type of the illness. Disclosure and advertising of another medication for the most part takes billions of dollars and up to 15 years(Bates, 1995) .

The development of nano delivery systems will provide an opportunity to exploit the inhalatory route, which has particular interest in the release of anti-TB drugs directly on the primary organ affected by TB (i.e., lungs). Thereby, it is possible to achieve a high local concentration of drugs in alveolar macrophage, a reduction of systemic adverse effects of the drugs as well as the frequency of administration, which ultimately leads to the increase of patient compliance and better efficacy of treatment (Almeida, et al., 2007; Pham, et al., 2015). In this context, the present work provides an overview on the recent progress in nano delivery systems for macrophage administration of anti-TB drug, discussing the draw backs of current treatment; the advantages of pulmonary delivery and macrophage delivery; different types of Nano delivery systems for encapsulation and release of anti-TB drugs, and the challenges that must be overcome to obtaining a more effective and compliant therapy. This prompts poor disintegration of rifabutin in the gastrointestinal tract and thusly low in vivo drug exposure following oral administration. Thus, oral administration conveys a restricted measure of the medication is to the lungs, a noteworthy site of Mycobacterium tuberculosis (MTB) contamination. Besides, just a little portion of the neighbourhood

measurements in the (Kleiner, et al., 2014). In this way, it is conceivable that oral malabsorption brought about rifabutin focus far underneath the restorative range at the fundamental site of disease.

Some countries where reported a higher incidence of Tuberculosis and people prescribes Bacille Calmette-Guérin (BCG) vaccine for the purpose of procurement against tuberculosis. Currently, the aim of treatment for tuberculosis involves the combination of many sets of the drug, usually given from the first line (Jaramillo, 2008; Zech, et al., 1995). In continuation to identify which set of drug combination work best after confirmatory test provided by the lab, which leads to prescribing a different set of tablets for different time intervals. In the case of drug default in prescribed tuberculosis medicines and infection becomes arduous to treat sometimes and they would not be curing the tuberculosis infection for the longer time in single infected person target to kill germs that are involved in no impairment now but could break out years from now and become active tuberculosis (Dawson, 2017).

The conventional approach of designing and synthesis of new therapeutic molecules has been a very hard task due to the involvement of efforts, time and cost often to an unlimited extent and new drugs always carry a risk of unwanted pharmacological responses. Thus now it is the need of the hour to reorient the research strategies and to find out the alternate solutions. The academic community continues to play a vital role in the development of new drugs or new dosage forms of existing pharmaceutical products (Laxminarayan, et al., 2013).

In recent years transporting the drug molecules to the desired site in the biological systems has become a very specific and sophisticated area of pharmaceutical research. The role of the drug delivery system is no more limited to a drug package just meant for convenience and administration but to bring a required change in therapeutic efficacy and safety by carrying the drug molecules to the desired site in the most convenient manner. This approach allowed evolving the concept of new drug delivery systems, which has generated a hope to rejuvenate the old drugs by giving them new dimensions (Goldman, et al., 2007). This will not only add the therapeutic value to the proprietary drugs but also economic value to off potent drugs. The enormous benefits can be predicted from their new systems specially keeping a view on newly signed GATE treaty and proposed change in patent act. The evolution and development of ultra-refined machineries along with various techniques of very high performances have given a direction to fabricate new drug delivery systems (Garrison, 1931).

The sign of positive developments are clear enough when pharmaceutical industries have started bearing the name title based on these systems e.g. Nanotechnology Inc. (U.K.).

Through the rapid advances of recent years, the field of drug delivery has become a multidisciplinary science which may be classified as:

1. Site specific drug delivery systems.
2. Implantable drug delivery systems.
3. Other non-invasive delivery systems.

The appearance of novel systems like the hydro-dynamically balanced systems, polymer coated drugs, ion exchange resin complex, mucoadhesive coating, osmotic pump and coating particulate systems, (Müller-Goymann, 2004) .

Rifabutin (Rfb) is an antibiotic used to treat tuberculosis and prevent and treat Mycobacterium avium complex. It is typically only used in those who cannot tolerate rifampin such as people with HIV/AIDS on antiretrovirals. For active tuberculosis it is used with other antimycobacterial medications. For latent tuberculosis it may be used by itself when the exposure was with drug-resistant TB (Gandhi, et al., 2010). Common side effects include abdominal pain, nausea, rash, headache, and low blood neutrophil levels. Other side effects include muscles pains and uveitis. While no harms have been found during pregnancy it has not been well studied in this population (Health, et al., 1990).

Rifabutin is in the rifamycin family of medications. Its mechanism of action is not clear. Rifabutin was approved for medical use in the United States in 1992. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Rifabutin is now recommended as first-line treatment for tuberculosis, but rifampicin was used more widely because of its cheaper cost. Rifabutin is used in the treatment of Mycobacterium avium complex disease, a bacterial infection most commonly encountered in late-stage AIDS patients(Caminero, et al., 2010). Its main usefulness lies in the fact that it has lesser drug interactions than rifampicin; therefore HIV infected patients on HAART are usually given rifabutin for treatment of TB. Rifabutin is well tolerated in patients with HIV-related tuberculosis (TB), but new findings suggest that patients with low CD4 cell counts have a high risk of treatment failure or relapse due to acquired rifamycin resistance. Since patients co-infected with TB and HIV/AIDS are likely to get TB treated first, when the CD4 is suppressed at the time TB treatment begins, doctors and patients should be aware of a possible rifamycin resistance (Meintjes, et al., 2009).

Rifabutin is also being investigated in trials for treating Crohn's disease as part of the anti-MAP therapy. In a Phase III study administering sub-therapeutic doses of rifabutin in combination therapy to patients not identified with MAP infections, it was associated with significant short term benefits. It has also found to be useful in the treatment of Chlamydophila pneumoniae (Cpn) infection. Rifabutin is primarily bactericidal antibiotic drug used to treat tuberculosis. Its effect on bacteria is based on the DNA-dependent RNA polymerase blocking drug rifamycin S, a semi-synthetic derivative. It is effective, for example, in highly resistant mycobacteria, Gram-positive bacteria (and some are effective against Gram-negative bacteria), but also against Mycobacterium tuberculosis, M. leprae, and M. avium intracellular (Oddo, et al., 1998).

Today, nanotechnology is a commonly used buzzword in numerous fields of science and everyday life, and fairly recently in drug delivery. Numerous definitions have been coined to describe nanotechnology and nanoscience and these are often used interchangeably. Nanoscience could be defined as the activity aimed at the understanding of natural laws at a nanoscale level and nanotechnology as the novel and practical applications of this scientific knowledge to change the world we live in. Several restrictions have been placed on what exactly nanotechnology is. It has been described as the exploitation of materials with structural features at the intermediate range between atoms and the molecular scale with the important prerequisite that at least one dimension is in the nanometre length scale. The most common consensus, however, is that nanotechnology investigates and manipulates materials and phenomena where at least one length scale is below 100 nm (Oddo, et al., 1998).

Nanotechnology in tuberculosis for the treatment, diagnosis, monitoring, and control of biological systems is referred to as "nanomedicine" by the National Institutes of Health. The potential of nanomedicine includes the development of nanoparticles for diagnostic and screening purposes, DNA sequencing using nanopores, manufacture of drug delivery systems and single-virus detection (Broz, et al., 2006). Nanotechnology has opened new vistas in biomedical research and the role of novel drug delivery systems for antimicrobial agents has been particularly impressive. Starting with the simple β-lactam antibiotics such as ampicillin and amoxicillin, the state-of-the-art now describes the controlled release of virtually all the classes of antimicrobials including antileishmanials, antifungals, anthelminthics, antivirals and antituberculars (Giddens, 2008). Mononuclear phagocytes, dendritic cells, endothelial cells and cancers cells are the key targets as far as

nanotechnology based drug delivery are concerned. The essential difference between micro and nanoparticles is not merely the size but also the ability of nanoparticles to achieve a higher drug encapsulation and enhance the bioavailability of orally administered drugs. In general, the smaller the particle size, the better is their absorption through the epithelium. Novel Delivery System is known to cross the intestinal permeability barrier directly via transcellular/paracellular pathways that explain the better delivery of the encapsulated drugs into the circulation. Several methods have been developed by researchers to obtain particles in the nano-size range (Alam, et al., 2010).

In the last decades the Nanoparticles can be obtained by polymerization of monomers entrapped the drug molecules, as well as from the preformed polymers. However, commonly the preformed polymers are used to prepare PLGA nanoparticles. The basic methodologies of commonly used preparation methods are-emulsion/evaporation, high-pressure emulsification solvent evaporation, double emulsion/evaporation, salting out, emulsification-diffusion, solvent displacement/nanoprecipitation, emulsion diffusion-evaporation etc. The subcutaneous and intramuscular routes provide bioavailability profiles close to the intravenous route. An important attribute of PLG nanoparticles was a high chemotherapeutic efficacy following subcutaneous administration (Pandey, et al., 2006).

A single injection of drug loaded PLG-nanoparticles resulted in sustained drug levels in the plasma for 32 days and in the organs for 36 days. There was a complete bacterial clearance from the organs of TB infected mice with a single dose of the formulation thereby proving its better efficacy compared with injectable PLG microparticles. PLG polymers are biodegradable, biocompatible and non-immunogenic in humans. Therefore these polymers can be repeatedly administered without adverse effects. PLG has a long history of safe use in humans as sutures, bone replacements and dental repairs etc. These observations thus further support the application of PLG-based nanotechnology for mycobacterial infections (Pandey, et al., 2006).

Based on above discussion, the present work was proposed to develop Nano Lipid Carrier of Rifabutin for enhancement of bioavailability and reduction in its side effects. Further, nano lipid carrier of rifabutin was planned to be developed for targeting of rifabutin to the macrophage cell. The cell line study also investigate the macrophage cell where also processed to access the targeting ability of the formulation (Hillaireau, et al., 2009).