Recent Advances in Nanotechnology based Tubercular Chemotherapy

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ABSTRACT

Tuberculosis (TB) is a more prevalent granulomatous bacterial infection, which remains the world’s second most common cause of death due to infections of Mycobacterium tuberculosis (M.Tuberculosis). A number of characteristics of mycobacterium makes there disease chronic and necessitate prolonged treatment. The emergence of multi-drug-resistance (MDR) stains of M.Tuberculosis makes its necessary for the development of effective combinations of either first-line or second-line drugs or discovery of new safe and effective drug molecules and also implements other modalities of treatment. A number of novel carrier-based drug delivery systems incorporating the traditional and newer anti-tubercular agents have been shown incredible promise to target the site of action, reduce dosing frequency and enhance drug bioavailability with the objective of improving patient compliance. Nanoparticulate system have unique and comparatively more effective drug delivery carriers, including liposomal-mediated drug delivery, polymeric nanoparticles/microparticles, solid lipid nanoparticles, nanosuspensions, niosomels, dendrimers, Metal/cyclodextrin inclusion complexes and other nanosystems exploiting the extraordinary properties of matter at the nanoscale. Nanoparticles shown significant improvements in diagnosis, treatment and prevention and provide the flexibility of selecting the invasive and non-invasive route of delivery for chemotherapy of tuberculosis. This manuscript has been made to highlight and overviews the present WHO estimated burden of tuberculosis globally, recent discovery of safe and effective newer anti-tubercular drug molecules for MDR and XDR tuberculosis, first and second line anti-tubercular drugs loaded novel nanoparticle carriers for chemotherapy and development of solid lipid nanoparticles as an alternative drug carriers for tubercular chemotherapy.

KEYWORDS: Tuberculosis, multi-drug-resistance, SLNs, liposomes, polymeric nanoparticles, nanosuspensions, niosomels, niosomes, dendrimers and Metal/cyclodextrin inclusion complexes.

Introduction

Tuberculosis (TB-Tubercle bacillus) is also known as phthisis, phthisis pulmonalis or consumption. TB is a leading chronic disease infected by M. Tuberculosis (Kumar et al., 2007). India is the second most populous country in the world and one-fourth of global incidence TB cases were found annually. In 2012, WHO estimated global annual incidence of 8.6 million TB cases and approx 2.3 million were estimated in India (Fig. 1) (TB annual report, 2014). India’s TB control programme RNTCP (Revised National Tuberculosis Control Programme) has been estimated that 42% reduction in mortality rate, 51% reduction in TB prevalence rate and 19% reduction in TB incidence rate by 2012 as compare to 1990 level (Fig. 2). Globally, WHO estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320000 deaths among HIV-positive people). The number of TB deaths is unacceptably large given that most are preventable. Nearly 20 years after the WHO declaration of TB as a global public health emergency, major progress has been made towards 2015 global targets set within the context of the Millennium Development Goals (MDGs). Two years ahead of the deadline, the Global “Tuberculosis Report 2013” and accompanying supplement “Countdown to 2015” assess progress towards the 2015 targets and the top priority actions needed to achieve and/or move beyond them (Global tuberculosis report, 2013).

Tuberculosis is still major health problems in many developing countries worldwide because of drug resistant TB, as its treatment is longer and requires more expensive drugs. Primary-resistance occurs when a person infected with a resistance stain of TB and the

ABBREVIATIONS: INH: Isoniazid; RIF: Rifampicin; PYZ: Pyrazinamide; EMB: Ethambutol; EE: Entrapment efficiency; CFUs: Colony forming units; PLG: Poly(DL-lactide-co-glycolide); PBCA: poly(butyl-2-cyano-acrylate); MIC: Minimum inhibitory concentration; ATDs: Antitubercular drugs; MCC-TETA: macrocyclic compound 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetra-acetic acid; FRET: Picosecond resolved Förster resonance energy transfer.
Secondary-resistance or acquired-resistance may develop when a person fully susceptible TB during therapy because of inadequate treatment, using low quality medicine, inappropriate regimen or lack of compliance (O’Brien, 1994).

WHO expert group has framed clear treatment guideline (after several years of experience) in 1997 for different categories of TB patients. The dose of first-line anti-TB drugs has been standardized on body weight basis and is applicable to both adults and children. All regimens have an initial intensive phase, lasting for 2–3 months aimed to rapidly kill the TB bacilli, bring about sputum conversion and afford symptomatic relief. This is followed by a continuation phase lasting for 4–6 months during which the remaining bacilli are eliminated so that relapse does not occur. Treatment of TB is categorized by:

- **Site of disease (pulmonary or extra-pulmonary) and its severity:** The bacillary load and acute threat to life or permanent handicap are taken into consideration.

- **Sputum smear-positive/negativity:** Positive cases are infectious and have higher mortality.

- **History of previous treatment:** Risk of drug resistant is more in irregularly treated patient. The category-wise treatment regimens are summarized below (Tripathi, 2010).

**Category I:** This category includes.

- New (untreated) smear-positive pulmonary TB.
- New smear-negative pulmonary TB with extensive parenchymal involvement.
- New case of severe forms of extrapulmonary TB, viz. meningitis, military, pericarditis, peritonitis, bilateral or extensive pleural effusion, spinal, intestinal, genitourinary TB.

**Category II:** These are smear-positive failure, relapse and interrupted cases:

- **Treatment failure:** Patient who remains or again becomes smear-positive 5 months or later after commencing treatment. Also one who smear-negative at start of therapy and becomes smear-positive after the 2nd month.

![Fig. 1. WHO estimated burden of TB in India.](Image)

![Fig. 2. Tuberculosis burden as incidence, prevalence and mortality per lakh population has reduced from year 1990 to year 2012.](Image)
Relapse: A Patient declared cured from any form of TB in the past after receiving one full course of chemotherapy and now has become sputum positive.

Treatment after interruption (default): A patient who interrupts treatment for 2 months or more and returns with sputum-positive or clinically active TB. These patients may have resistant bacilli and are at greater risk of development MDR-TB.

Category III: These are new cases of smear-negative pulmonary TB with limited parenchymal involvement or less severe forms of extrapulmonary TB, viz. lymphnode TB, unilateral pleural effusion, bone (excluding spine), peripheral joint or skin TB.

Category IV: These are chronic cases that have remained or have become smear-positive after completing full supervised retreatment (category II) regimen. These are more likely MDR case.

Barriers in Conventional Chemotherapy of Tuberculosis

There are various barriers in conventional therapy of tuberculosis. These barriers are discussed in details:

(i) Poor bio-distribution at cellular level: Effective therapeutic concentration at target site is difficult to achieve in traditional chemotherapy because drugs also have high affinity to other body tissues and serum proteins, which may also leads to increase in systemic toxicity (Ratin and Mick, 1996).

(ii) Chemotherapy associated side effects: In traditional chemotherapy side effects are measured and reported and it may be acute, chronic or permanent and may cause anemia, alopecia, depression, low blood counts, mouth sores, nausea and vomiting, neutropenia, thrombocytopenia and life threatening or fatal. The side effects are associated with first line drugs i.e., rifampicin, isoniazid, pyrazinamide and ethambutol can cause nausea, vomiting, skin rash, peripheral neuropathy, hepatotoxicity, blurred vision, inability to distinguish colors and more rarely anemia and pellagra (Lowenthal and Eaton, 1996).

(iii) Drug resistance tuberculosis: Resistance to chemotherapy can be developed at cellular or non-cellular level which results to decrease therapeutic concentration at the target site. The multi-drug-resistance TB (MDR-TB) is defined as resistance to the two most effective first-line TB drugs i.e., rifampicin and isoniazide (O’Brien, 1994). The emergence of MDR-TB because mycobacteria grow slowly and may be dormant in the host for long period, thus they are relatively resistant to the effects of antibiotics. As a consequence, effective therapy of TB infection requires a prolonged course i.e., months to years of multiple drugs. Issues of drug toxicity and patient compliance are important (Tripathi, 2010). Extensively drug resistance TB (XDR-TB) is also resistant to three or more of the six classes of second-line drugs (CDCP, 2006). Totally drug resistance (TDR-TB) is resistance to all current used drugs. It was first observed in 2003 at Italy, but not widely reported until 2012.

The following ways the TB acquires drug resistance are: (Louw et al., 2009)

Cell wall: M.Tuberculosis cell wall consists of complex lipids and acts as a permeability barrier.

Drug modifying and inactivating enzymes: The M.Tuberculosis genomes code for certain enzymes usually phosphorylate, acetylate or adenylate the drug complex which makes drug resistance.

Mutation: Spontaneous mutation in the M.Tuberculosis genome that makes the bacterium drug resistance, depending on the drug action.

The emergence of drug-resistance of M.Tuberculosis makes it necessary to consider the general prevention during chemotherapy, discovery of new molecules and the current situation even necessitates the re-engineering and repositioning of some old drug families to achieve effective control.

General preventions: (LoBue and Philip, 2009; Gao and Li, 2010).

There are several ways that drug resistance to TB and drug resistance in general can be prevented.

Rapid diagnosis and proper treatment of TB: One of the major risk factor to diagnose and treatment in developing countries. Resistance TB can be avoided by early identify and treated as early as possible.

Completion of treatment: Previous treatment of TB is an indicator of MDR-TB because of incomplete antibiotic treatment by patient or does not prescribe the proper dosage regimen by physician. Antibiotics that are of poor quality or less in quantity can contribute to MDR-TB.

Patient with HIV/AIDS: The patients infected with HIV/AIDS have lack of immunity to fight against TB infection and are great risk of developing drug resistance.

Identify contacted TB: Identify contacts who could have contacted TB i.e., family members, and people in close contact etc.

Research: More and more research and funding are needed in diagnose, prevention and treatment of TB and MDR-TB.

Discovery of safe and effective new anti-TB drug molecules: There are two ways to overcome such situations, first approach is to discovery safe and effective new drug molecule with negligible side effect with long half lives and large therapeutic indices. Second approach is to development of better, safe and effective pharmaceuticals of existing drug through newer concept and techniques. The first approach is arduous, lengthy, time consuming and remain extremely difficult to
identify new compounds (Brahmankar and Jaiswal, 2004).

The current chemotherapy of tuberculosis dates back to the 1950s and is lengthy and extremely difficult to complete the treatment. Nowadays, many of the newer drug molecules like oxazolidinones (Linezolid), fluoroquinolones, beta-sulfonylecarboxamides, capuramycins (RS 118641), erythromycin, pleuromutilin and various other semisynthetic derivatives of rifampicin (rifapentine, rifalazil, rifabutin and rifametane etc.) are under pipeline in various phases of trial, these newer molecules showed promising activity against sensitive and resistant TB stains in clinical trials or preclinical development (Gutierrez-Lugo and Bewley, 2008). Table 1, shows some of the newly identified drug molecules which are effective against TB and MDR-TB.

**New Carriers for chemotherapy:** Over the last few decades, the applications of nanotechnology based carrier system makes an important impact on clinical practice, not only in the field of target drug delivery but also for the delivery of diagnostic agents, gene therapy, vaccines, improve permeability and bioavailability as well. The nano-carrier systems have been extensively explored in medicinal field, especially in drug delivery. Nanoparticles size 1-100 nm scale have unique physiochemical features including ultra small size, large surface area, to mass ratio high reactivity and unique interactions with biological systems (Zhang et al., 2010). They have numerous advantages in drug delivery science, including improving serum solubility of the drugs, prolonging the systemic circulation life time, releasing drugs at a sustained and controlled manner, preferentially delivering drugs to the tissues and cells of interest and concurrently delivering multiple therapeutic agents to the same cells for combination therapy (Zhang et al., 2010; Pandey et al., 2004; Pandey et al., 2004a).

### TABLE 1

<table>
<thead>
<tr>
<th>Drugs already in use:</th>
<th>Conclusions and Activities</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Gatifloxacin</td>
<td>Studies under clinical phase II and III trials showed, these drugs are also effective in the use of tuberculosis to shorten the treatment from the standard 6-9 months.</td>
<td>Weiner et al., 2007</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Higher dose of rifampicin and their derivatives is more effective in the chemotherapy of TB. Limited data available on a higher dose.</td>
<td>Jayaram et al., 2003</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Fluoroquinolones are registered as second line anti-TB drugs. They are more effective against intracellular mycobacterium.</td>
<td>Drlica et al., 1998; Gillespie et al., 1998; Paramasivan et al., 2003; Stein, 1996</td>
</tr>
<tr>
<td>Rifamycin A,B,C,D etc. and derivative of Rifamycin B (Rifampicin, Rifabutin, Rifamide)</td>
<td>Oxazolidinones are under the phases of clinical trials. However, limited clinical trials data are available for MDR and XDR-TB</td>
<td>Tangg et al., 2011</td>
</tr>
<tr>
<td><strong>Newer drug molecules:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Diaryquinolines: R207910 (Johnson &amp; Johnson) or TMC-207 or Compound J (Tibotec)</td>
<td>Newer active molecules (diaryquinolines) under clinical phase II trials showed active against susceptible and MDR-stains.</td>
<td>Ibrahim et al., 2007; Reddy et al., 2010; De-Jonge et al., 2007</td>
</tr>
<tr>
<td>Nitroimidazoles: PA-824 (Prodrug) (Otsuka Pharmaceuticals), OPC-67883</td>
<td>Under the studies of clinical trials showed, they are active in susceptible and resistant TB-stains and could be useful in treatment of MDR and XDR-TB.</td>
<td>Stover et al., 2000; Otsuka Pharm, 2012</td>
</tr>
<tr>
<td>Diamines: SQ 109 SQ 609 (Sequella Inc.)</td>
<td>Under preclinical and phase II clinical trials showed the synergistic activity against rifampicin resistant stains.</td>
<td>Jia et al., 2005; Sequella, 2007</td>
</tr>
<tr>
<td>Pymrole derivative: Sudoterb or LL-3858</td>
<td>Bactericidal activity against both drug sensitive and MDR-TB investigated in phase I clinical trials.</td>
<td>Deidda et al., 1998; Arora et al., 2004</td>
</tr>
<tr>
<td>Oxazolidinones: PNU100480 (Pfizer) AZD5847 (AstraZeneca)</td>
<td>Greater efficiency of newer oxazolidinones was evaluated in phase I clinical trials (in-vitro studies) as compare to Linezolide.</td>
<td>Sequella, 2010; AstraZeneca, 2010</td>
</tr>
<tr>
<td>Benzothiastinone: BTZ-043 (NMTB Consortium)</td>
<td>The preclinical studies determine the future direction of the development.</td>
<td>Yadav et al., 2012</td>
</tr>
<tr>
<td>Sulfoamyl triamide: FAS-20013 (From FASgen)</td>
<td>Investigated in clinical trials that they are active against MDR-TB and expected to be effective against dormant bacteria.</td>
<td>Yadav et al., 2012</td>
</tr>
<tr>
<td>Pyrroles: LL-3858 (Lupin)</td>
<td>Investigated in phase I clinical trial that LL-3858 is active against M. Tuberculosis stains that are resistant to available anti-TB drugs.</td>
<td>Alqahtani and Aasad, 2014</td>
</tr>
<tr>
<td>CPZEN-45 (Lilly)</td>
<td>The results of preclinical studies determine the future direction of the development.</td>
<td>Bogatcheva et al., 2007</td>
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</table>
Chemotherapy of tuberculosis needs multidrug regimens of first line anti-tubercular drugs for long duration. Anti-tubercular chemotherapy shows: poor patient compliance, Poor bio-distribution, chemotherapy associated side effects and resistant tuberculosis is the most common reason for the failure of tubercular chemotherapy (CDCP, 2006; Prabakaran et al., 2004). Over the last few decades, the applications of nanotechnology have been extensively explored in the chemotherapy of tuberculosis to overcome the failure of chemotherapy and improve patient compliance, this is because of unique physicochemical properties including ultra size range, larger surface to mass ratio, high reactivity and unique interactions with biological system. Drug loading into nanoparticles can be significantly improved the pharmacokinetics and therapeutic index of the drug in contrast to the free drug counterpart. Various advantages of nanoparticles based drug delivery have been observed including, high serum solubility, prolong lifetime systemic circulation and release drugs at a sustained and controlled manner, drug deliver to the tissue and cell of interest and concurrently delivery of multiple drugs to the same cells for combination therapy. Drug loaded nanoparticles can enter into the host cell via endocytosis and then release drug payload to treat microbes-induced intracellular infections. As a result, a number of nanoparticles based drug delivery have been approved for clinical tests (Zhang et al., 2010). Nanoparticulate system have unique and comparatively more effective drug delivery carriers, including liposomal-mediated drug delivery, polymeric nanoparticles/microparticles, solid lipid nanoparticles, nanosuspensions, nanoemulsions, niosomes, dendrimers, cyclodextrin inclusion complexes and other nanosystems exploiting the extraordinary properties of matter at the nanoscale. Nanoparticles shown significant improvements in diagnosis, treatment and prevention and provide the flexibility of selecting the invasive and non-invasive route of delivery for chemotherapy of tuberculosis. The researchers have much interest in nano-drug carriers as higher stability and carrier capacity along with immense improvement of drug bioavailability which further leads to reduction in dosing frequency.

**Novel technologies for tuberculosis**

**Liposomes:** Liposomes are small spherical vesicles with a bi-layered membrane composed of natural or synthetic amphiphilic lipids. They can be coated with polymers for stabilization of the structure and to prolong circulation half-life, or functionalized with specific ligands for targeted cell or organ delivery. Their unique ability to encapsulate both hydrophobic and hydrophilic drugs makes them excellent as therapeutic carriers (Griffiths et al., 2010). They are non-toxic, biodegradable, biocompatible, target drug delivery, controlled/sustained release, stability, feasibility of intravenous and nebulization property makes them attractive candidates for the delivery of antitubercular drugs (Pandey et al., 2004; 2004a). However, research in the field of mycobacterial diseases using liposomes is evolved through several phases that are from laboratory to the clinical studies (Khuller et al., 2004). Drugs encapsulated liposomes are reported in literature used for the mycobacterium infection (Table 2).

**TABLE 2**

Drugs encapsulated liposomes used for mycobacterium infection.

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Target site/ Microorganisms</th>
<th>Exp. Model/ In vitro/ In vivo Studies</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF (Inhalation)</td>
<td>Target to alveolar macrophages</td>
<td>Murine TB model</td>
<td>Maintained therapeutic drug concentrations in plasma for 48 hr whereas free rifampicin was cleared by 24 hr. Liposomal drug was present in the lungs and more importantly in the alveolar macrophages till day 5 post-nebulization.</td>
<td>Kurunov et al., 1995</td>
</tr>
<tr>
<td>Gentamicine (IV)</td>
<td>Mycobacterium avium complex infection</td>
<td>Mouse model</td>
<td>Improve drug bioavailability and reducing dosing frequency. Significant improvement in the pharmacokinetic parameters.</td>
<td>Klemens et al., 1990</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>Mycobacterium avium</td>
<td>Murine macrophage-like cell line J774</td>
<td>Improve therapeutic efficacy as compared to free drug.</td>
<td>Düzgünğını et al., 1996</td>
</tr>
<tr>
<td>Streptomycin (IV)</td>
<td>Mycobacterium avium</td>
<td>Beige mice</td>
<td>Liposome encapsulation resulted in several-fold increase in the chemotherapeutic efficacy.</td>
<td>Gangadhamram et al., 1991</td>
</tr>
<tr>
<td>Amikacin (IV)</td>
<td>Mycobacterium avium</td>
<td>Murine model</td>
<td>Result showed high and sustained drug level in infected tissues, exceeding the minimal inhibitory concentration for M_Avium for at least 28 days. Reduced the bacterial counts in the livers by more than 2 orders of magnitude.</td>
<td>Leitzke et al., 1998</td>
</tr>
<tr>
<td>INH, PYZ, RIF, Ethionamide, and Streptomycin (Inhalation)</td>
<td>-</td>
<td>-</td>
<td>Showed a satisfactory drug loading for INH as well as PYZ as compare to the encapsulation of RIF, streptomycin and ethionamide.</td>
<td>Justo and Moraes, 2003</td>
</tr>
</tbody>
</table>

TABLE 2 Contd...
### Drug(s) Target site/ Microorganisms Exp. Model/ In vitro/ In vivo Studies Activity References

**Ciprofloxacin and Azithromycin**  
*Mycobacterium avium*  
Murine macrophage-like cell line J774  
- Enhanced antmycobacterial effect in liposomes.  
- Ciprofloxacin or azithromycin encapsulated in stable liposomes.  
Oh et al., 1995

**INH and RIF (Nebulizer)**  
*Mycobacterium tuberculosis*  
Guinea pigs  
- Liposomes encapsulated RIF and INH drugs in guinea pigs and found the loaded rifampicin was better compared with isoniazid.  
Pandey et al., 2004a; Vyas et al., 2004

**INH and RIF**  
*Mycobacterium tuberculosis*  
Mice  
- Liposomes were less toxic to peritoneal macrophages as compared to free drugs.  
- Therapeutic dose of encapsulated-INH and RIF led to a sharp decrease in colony forming units in lungs, liver and spleen as compare to free drugs.  
Deol and Khuller, 1997; Deol et al., 1997

**Clofazimine & Resorcinomycin**  
*M. Avium/ M.Tuberculosis* Culture strains  
- Seven of 19 agents were selected for incorporation into liposomes. Clofazimine and Resorcinomycin A had the highest killing effects (MBC90s, 8 and 16 micrograms/mL, respectively).  
Mehta et al., 1993

**Clofazimine**  
*Murine Tuberculosis*  
Mice  
- The result showed a significant CFU reduction in all tissues without any toxic effects.  
Adams et al., 1999

**PYZ (Oral)**  
*Mycobacterium tuberculosis*  
Mice  
- Highly significant reduction in bacterial counts (CFU s/g lung).  
- The results indicate high therapeutic efficacy of PYZ liposomes, injected twice weekly, in treatment of *M. Tuberculosis* in mice  
El-Ridy et al., 2007

**Rifabutin (IV)**  
*Mycobacterium tuberculosis*  
Mouse model  
- Concentrations of the antibiotic were achieved in liver, spleen and lungs 24 hr post administration compared with free Rifabutin.  
- Results suggest that liposomal Rifabutin is a promising approach for the treatment of extrapulmonary TB in HIV patients  
Gaspar et al., 2008

### Niosomes: Niosomes are similarly as liposomes and they are manly composed of non-ionic surfactants and with or without incorporation of lipids. They are biodegradable, biocompatible and nonimmunogenic in nature can be used to deliver hydrophilic drugs in its aqueous core and lipophilic drugs in the bilayer made up of surfactants. The non-ionic surfactants are the major components in niosomes, which give it an advantage of being more thermodynamically stable, thus overcome the problems such as high price, susceptibility to oxidation, difficulty in procuring high purity levels which influence size, shape and stability associated to liposomes (Sankhyan and Pawar, 2012). The niosomes drug delivery systems have been exploited for their maximum therapeutic utilization in management of tuberculosis (Table 3).  

### Polymeric nanoparticles: Langer and Folkman, first developed polymer based drug delivery system in 1976 for macromolecular delivery. Initially, polymeric nanoparticles (PNPs) possessed poor therapeutic efficacy after intravenous administration (Langer and Folkman, 1976). This drawback was overcome by Gref et al., 1994, after discovery of stealth polymeric nanoparticles (Gref et al., 1994). Polymer based deliveries have found wide biomedical applications by using synthetic (e.g. polylactide-co-glycolide) and natural polymers (e.g. alginate, chitosan etc.). This technology is used to generate two kinds of systems: nanocapsules and nanospheres by using biocompatible/biodegradable polymers. These are extensively explored due to several unique characteristics: Firstly, PNP s are structurally stable and can be synthesized with a sharper size distribution. Secondly, particle properties such as size, zeta potentials, and drug release profiles can be precisely tuned by selecting different polymer lengths, surfactants, and organic solvents during the synthesis. Thirdly, the surface of polymeric nanoparticles typically contains functional groups that can be chemically modified with either drug moieties or targeting ligands(Zhang et al., 2010). ATDs either single or in combinations can be encapsulated in polymers to provide controlled drug release and the system also offers the flexibility of selecting various routes of administration such as oral, subcutaneous and aerosol and eliminated from the body by opsonization and phagocytosis(Pandey and Khuller, 2004). This approach is one of the most extensively investigated with respect to encapsulation of antitubercular drug listed in Table 4.
TABLE 3
The niosomes encapsulated antitubercular drugs.

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Target site/ Microorganisms</th>
<th>Exp. Model/ In vitro/In vivo Studies</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF (IV and Intraperitonial)</td>
<td>Mycobacterium tuberculosis</td>
<td>Wistar rats</td>
<td>• Niosomal encapsulation RIF results in controlled drug release and can reduce drug dose, dosing frequency and toxicity which may result into improved patient compliances.</td>
<td>Jain and Vyas, 1995; Jain et al., 2006; Singh et al., 2010; Alladi et al., 2010</td>
</tr>
<tr>
<td>EMB hydrochloride</td>
<td>Mycobacterium tuberculosis</td>
<td>Mice and Guinea pigs</td>
<td>• Lung targeting was increased by niosomal encapsulation. • Niosomal encapsulation results in controlled drug release and biological evaluation revealed superiority of niosomal EMB hydrochloride over the free drug.</td>
<td>El-Ridy et al., 2011; 2015</td>
</tr>
<tr>
<td>INH</td>
<td>-</td>
<td>In vitro studies</td>
<td>• The niosomes demonstrated a potential to remain in the treated site for prolonged periods and were also capable of maintaining steady drug concentrations for up to 30 hr.</td>
<td>Singh et al., 2011</td>
</tr>
<tr>
<td>PYZ</td>
<td>-</td>
<td>In vitro studies</td>
<td>• In vitro release studies were carried out for all formulations and it was seen that Span-80 formulation had the highest percentage release as compared to other formulations. • The drug release was subjected to various kinetic models and it was observed that all formulations followed zero order kinetics.</td>
<td>Thomas and Bagyalakshmi, 2013</td>
</tr>
<tr>
<td>RIF, INH and PYZ</td>
<td>-</td>
<td>In vitro studies</td>
<td>• The results showed Fickian or diffusional release for RIF and INH and a non-Fickian release mechanism for PYZ. • The efficiency of these drugs in the niosomes has high encapsulation efficiency and stability.</td>
<td>Mehta et al., 2011</td>
</tr>
<tr>
<td>RIF and Gatifloxacin</td>
<td>Mycobacterium tuberculosis</td>
<td>In vitro and in vivo studies</td>
<td>• RIF and gatifloxacin niosomes showed a nano-vesicle size range of 100-300 nm, % EE were 73% and 70% and in vitro release study showed that 98.98% and 97.74% respectively. • The study on resistant strains (RF 8554) and sensitive strains (H37Rv) of Mycobacterium tuberculosis showed greater inhibition and reduced growth index.</td>
<td>Rani et al., 2010</td>
</tr>
<tr>
<td>INH</td>
<td>Mycobacterium tuberculosis</td>
<td>Albino rats</td>
<td>• In vitro release pattern indicate sustained drug release for 48 hr and lesser toxicity in vivo than free drug.</td>
<td>Karki et al., 2008</td>
</tr>
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</table>

TABLE 4
The polymeric nanoparticles/microparticles encapsulated antitubercular drugs.

<table>
<thead>
<tr>
<th>Polymeric encapsulated-ATDs.</th>
<th>Target site/ Microorganisms</th>
<th>Exp. Model/ In vitro/in vivo Studies</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLG–nanoparticles–RIF, INH &amp; PYZ (Inhalation, Oral)</td>
<td>Mycobacterium tuberculosis</td>
<td>Guinea pigs</td>
<td>• Improving drug bioavailability and • Reducing dosing frequency and dose.</td>
<td>Pandey et al., 2005; Sharma et al., 2004</td>
</tr>
<tr>
<td>PLG–microparticles–ATDs (Oral)</td>
<td>Mycobacterium tuberculosis</td>
<td>-</td>
<td>• Improving pharmacokinetics • Microparticles were tested and found to be less effective as compared to nanoparticles.</td>
<td>Ain et al., 2002</td>
</tr>
<tr>
<td>PLG–microparticles–INH &amp; RIF (Oral)</td>
<td>Mycobacterium tuberculosis</td>
<td>Murine model</td>
<td>• Sustained drug release • Improvement for tuberculosis chemotherapy over the conventional treatment</td>
<td>Dutt and Khullar, 2001</td>
</tr>
<tr>
<td>Lectin–PLG–nanoparticles-RIF, INH &amp; PYZ (Oral, Inhalation)</td>
<td>Mycobacterium tuberculosis</td>
<td>Guinea pigs</td>
<td>• Showed bioadhesion and increase in relative bioavailability • Reduce the drug dosage frequency and improve patient compliance • Drugs were present in lungs, liver and spleen for 15 days</td>
<td>Sharma et al., 2004a</td>
</tr>
</tbody>
</table>
Nanoemulsions: One of the nanoscience approaches that has receiving an increasingly considerable attention within the pharmaceutical sciences is the formulation as nanoemulsions, mostly oil-in-water (O/W) type as an alternative and effective dosage forms for poorly water-soluble drugs, in which these active pharmaceutical ingredients may be dissolved into dispersed phase of the emulsion. Nanoemulsions are usually homogenous mixture consisting of various oils and/or fats dispersed throughout the continuous phase in the presence of an emulsifying agent that are “Generally Recognized as Safe” (GRAS) by FDA (Constantinides et al., 2008). Nanoemulsion formulations are extensively studied for their potential application as multifunctional nanocarriers with the mean droplet diameters ranging from 50 to 1000 nm, which allow for the variety of infectious diseases and chemotherapies. However, the preparation of nanoemulsions can be a challenge such as color, appearance, texture, rheology and stability are greatly affected by emulsion droplet size. However, their long term physical stability associated with small nanosized droplet that enables the system to remain dispersed with no apparent flocculation or coalescence and therefore they are sometimes referred to as thermodynamic stable. Nanoemulsions are better and even superior than macroemulsions because of their versatile features and unique advantages. Formulations of nanoemulsion, increases drug solubility, rapid dissolution velocity and enhance bioavailability with reduced side effects after oral administration due to larger interfacial area to volume ratio (Ahmad et al., 2008). Over the recent years, interest has grown in the design and development of new dosage form of pharmaceutical nanoemulsions. Much has been reported about the lipophilic active ingredient into nanoemulsion dosage form as potential drug delivery system (Table 5).
**Dendrimers:** Dendrimers are three dimensional morphologically a novel class of structurally repeated branch macromolecules that radiate from central core and are mainly derived from branches-upon-branches (Shegokar et al., 2011). In 1978, the dendrimers are first well-defined and made by divergent synthesis approach (Buhleier et al., 1978) and by convergent synthetic approach and polypropylene imine (PPI) dendrimers, developed by Wörner and Mülhaupt, in 1993 and convergent synthetic approach was introduce by Fréchetin 1990. Tomalia et al., in 1984, reported a new class of dendrimers with a mixture of amines and amides commonly known as polyamidoamine (PAMAM) dendrimers. They have very strong potential for many applications like: conjugation with other chemical species to the dendrimer surface that can function as detecting agents, affinity ligands, targeting components, radio-ligands, imaging agents or pharmaceutically active compounds because their structure has hundreds of possible sites to couple to an active species. Researchers aimed to utilize the hydrophobic core and hydrophilic periphery to incorporate of drug molecules to the same dendrimer, which could reduce negative side effects of medications on healthy cells. Dendrimers have been explored due to physical characteristics of dendrimers, including their monodispersity, water solubility, encapsulation ability, and large number of functionalizable peripheral groups, make these macromolecules appropriate candidates for evaluation as drug delivery vehicles. However, three methods are using in drug delivery: In First method, the drug is covalently attached to the periphery of the dendrimer to form dendrimer prodrugs. In second method, the drug is coordinated to the outer functional groups via ionic interactions and in third method, the dendrimer acts as a unimolecular micelle by encapsulating a pharmaceutical through the formation of a dendrimer-drug supramolecular assembly (Tekade et al., 2009).

Dendrimers have great interest for drug delivery and have a very strong potential for tubercular chemotherapy and other applications because one dendrimer molecule has hundreds of possible sites to couple to an active species. Kumar et al., developed 4.0G EDA-PPI dendrimer-(NH2)32 and 5.0G EDA-PPI dendrimer-(NH2)64 using methoxypropylene glycol. PEGylation has been found to be suitable for modification of ethylene diamine initiator core EDA-PPI dendrimers-(NH2)64 for prolonged release of RIF. Mannose on surface significantly reduced the haemolytic toxicity of the nanocarriers from 15.6 to 2.8%. This hemolytic toxicity studies revealed that these systems are relatively safer and hold potential as delivery system for rifampicin for parenteral administration (Kumar et al., 2006; 2007a). More recent reports investigated fourth and fifth generation PEGylated-PPI dendrimers for significant increase in drug entrapment and sustain the delivery of RIF. PEG-grafted dendrimers showed low haemolytic activity (1–3%) as composed the NH2-terminated ones (14–20%) (Kaminskas et al., 2009). Researchers from Monash Institute of Pharmaceutical Science (Melbourne, Australia) developed PEGylated Polylysine dendrimers in collaboration with Starpharma Holdings Ltd for cancer, HIV, tuberculosis and lymphatic disease conditions (Manalan et al., 2014). Alternative experimental drug delivery systems and other applications, such as fullerenes (for example, carbon spheres, or ‘buckyballs’, and carbon nanotubes) and metallic nanoshells (for example, gold nanoshells), are under development and have not yet been reported as having a TB application (Griffiths et al., 2010).

**Metal/Cyclodextrin inclusion complexes:** In mycobacteria, the study of inhibition by metal ions has been limited by the absence of suitable molecular vectors. Although Inclusion complexes of drugs with cycloexetrins (CDs) one of the approaches has been proposed for the chemotherapy, Cyclodextrins are products of high added value that have found applications as carriers for therapeutic drugs because it may modify drug properties such as physicochemical stability and bioavailability. The inventions related to paramagnetic solid lipids

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**TABLE 5**

Nanoemulsion drug delivery system effective against mycobacterium tuberculosis.

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Target site/ Microorganism</th>
<th>Exp. Model</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capuramycin</td>
<td>Mycobacterium tuberculosis</td>
<td>Mouse macrophage cell line</td>
<td>* Capuramycin analogue-nanoemulsion formulations prepared using d-tocopheryl polyethylene glycol 1000 succinate as emulsifier showed significantly improved intracellular activity over free drug.</td>
<td>Reddy et al., 2011</td>
</tr>
<tr>
<td>SQ641 (IV)</td>
<td>Mycobacterium tuberculosis</td>
<td>Mouse macrophages</td>
<td>* SQ641-nanoemulsion reached peak concentrations in lung and spleen in 1 hr and show significantly reduction of CFUs of <em>M. Tuberculosis</em> in spleen and lungs.</td>
<td>Nikonenko et al., 2014</td>
</tr>
<tr>
<td>RIF (IV)</td>
<td>-</td>
<td>* In vitro studies*</td>
<td>* Entrapment efficiency was found to be 99% with excellent stability over 19 months and results indicated the potential of nanoemulsions for intravenous delivery of RIF.</td>
<td>Ahmad et al., 2008</td>
</tr>
<tr>
<td>Microemulsion--INH, PYZ &amp; RIF</td>
<td>-</td>
<td>* In vitro analysis*</td>
<td>* The result showed microemulsion appears beneficial for the delivery of the ATDs in terms of easy preparation, stability, low cost, sustained and controlled release of a highly water soluble drug.</td>
<td>Mehta et al., 2008, 2010</td>
</tr>
</tbody>
</table>

**Notes:**
- *: Significant difference
- Microemulsion--INH, PYZ & RIF: Microemulsion with INH, PYZ, and RIF
- Mouse macrophages: Mouse macrophages
- M. Tuberculosis: Mycobacterium tuberculosis
- *: Significant difference
nanoparticles comprising an antitubercular drug complexed with a paramagnetic metal ion selected from the group consisting of: Gd(III), Mn(II), Cr(III), Cu(II), Fe(III), Pr(III), Nd(III), Sm(III), Tb(III), Yb(III), Dy(III), Ho(III) and Er(III), or salts thereof (Ghiani et al., 2014). The Inclusion complexes are in aqueous drug delivery systems such as liposomes and paramagnetic solid lipid nanoparticles increase the efficacy and decrease side effects of drugs. These properties make complexation attractive candidates for improving the chemotherapy of tuberculosis (Lima et al., 1999). More recently non-side rophorechelators have been developed and tested against mycobacterial species showing enhanced activity when in the form of complexes. This approach is one of the most extensively investigated with respect to ATDs-complexes are listed in Table 6.

**TABLE 6**

Antitubercular drugs-Metal/Cyclodextrins inclusion complex active against *Mycobacterium tuberculosis*.

<table>
<thead>
<tr>
<th>Drug(s)-Metal complexes</th>
<th>Target site/ Microorganisms</th>
<th>Exp. Model/ in vitro / in vivo Studies</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
</table>
| Carboxamidrazones analogs–Cu(II) & Fe(III) complexes | *Mycobacterium tuberculosis* | In vitro studies | • Nine such carboxamidrazone analogs (L1–L9) along with their Cu(II) (MC1–MC9) and Fe(III) (MC10–MC18) complexes were synthesized.  
• The results show 32–64-fold enhancement in antitubercular activity upon copper complexation | Sandbhor et al., 2002 |
| MCC-TETA–In(III) & bismuth(III) | *Mycobacterium tuberculosis* | In vitro studies | • The highest radiometric inhibition levels were obtained with the [In(TETA)]⁻ complex, which caused drops of up to 4 log units in cellular viability. The minimal inhibitory concentration of this compound was evaluated at 3 μM. | David et al., 2005 |
| INH–Tc99m (IV) | *Mycobacterium tuberculosis* | Mice and Rabbits | • The radiolabeled complex was found to be 90% bound to blood protein resulting in long duration imaging advantage.  
• Organ distribution studies showed the renal route of excretion of Tc-99 m INH. No gastric or thyroid activity was noted, thereby suggesting high labeling efficiency and in-vivo stability.  
• Animal study suggest that Tc-99 m INH is a viable, specific and cost effective agent for diagnosis and localization of tubercular lesions. | Singh et al., 2003 |
| RIF–Warfarin Complex | - | - | • FRET from Warfarin to RIF explores possible binding sites of the anti-tuberculosis drug on the protein. In this study, found potential problem of using the single tryptophan of the protein as energy donor in FRET experiment for the characterization of the binding site of the drug RIF on the protein. | Rajdev et al., 2011 |
| EMB–Divalent metal cations | *Mycobacterium tuberculosis* | - | • Experimental studies shows that the (S,S)-configuration of EMB-metal complex is stable and essential for activity against *Mycobacterium tuberculosis*. | Ramalho et al., 2004 |
| INH–Rare earth metal ions | - | In vitro activity | • INH complex with rare earth metal ions like: La(III), Ce(III), Nd(III), Sm(III), Gd(III), Tb(III) and Dy(III) using PH - metric technique and thermodynamic parameter ΔG, ΔH and AS were calculated from values of stability constant at different temperatures and found order of stability constants for these metal complexes was as follows: La<Ce<Nd<Sm>Gd<Tb>Dy. | Thakur et al., 2012 |
| INH–Ni(II) | *Mycobacterium tuberculosis* | In vitro studies | • They MIC values ranging from < 0.1 to 0.39 mg/mL, showing them to be generally more active than previously reported analogous Cu(II) and Ni(II) complexes. | Bottari et al., 2001; 2001a; Maccari et al., 2004 |
| INH–Cr(III), V(IV) & Ti(III) | *Mycobacterium tuberculosis* | - | • The complexes of Cr(III) and Ti(III) showed significant tuberculostatic activity. | Pin and Zhang, 1989 |
and biocompatible surfactant (s) using various methods. SLN can be prepared by using lipid(s), waxes necessary stabilized with preferably 0.5% to 5% (w/w) avoidance of organic solvents etc (Kaur and Bhandari, 2013). SLNs are composed of 0.1% (w/w) to 30% (w/w) solid lipid dispersed in an aqueous medium and if necessary stabilized with preferably 0.5% to 5% (w/w) surfactant. SLN can be prepared by using lipid(s), waxes and biocompatible surfactant(s) using various methods reported in the literature (Mukherjee et al., 2009). SLNs have applications in drug delivery system, cosmetics and pulmonary has been proposed for the delivery of antitubercular drugs as Directly Observed Treatment Short course (DOTS) to eradicate the causative mycobacterium infection. However, it is currently out of reach because of the difficulty in diagnosis, inconvenience in treatment, long duration, high cost of therapy along with associated side effects and emergence of multi drug resistance. It is necessary to consider the general prevention during chemotherapy, discovery of new molecules and the current situation even necessitates the re-engineering and repositioning of some old antitubercular drugs. The controlled/sustained release and targeted delivery would make it possible to reduce dosing frequency, short duration of treatment thereby improve patient compliance. The novel

<table>
<thead>
<tr>
<th>Drug(s)/Metal complexes</th>
<th>Target site/Microorganisms</th>
<th>Exp. Model/ in vitro/in vivo Studies</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATDs–Oxovanadium(IV)</td>
<td>Mycobacterium fluo, smegmatis and H37Rv</td>
<td>In vitro activity</td>
<td>• Antitubercular activities of oxovanadium (IV) complexes with ATDs have been shown against tuberculosis mycobacteria such as Mycobacterium fluo, Mycobacterium smegmatis and Mycobacterium H37Rv.</td>
<td>Maiti and Ghosh, 1989</td>
</tr>
<tr>
<td>RIF–Cyclodextrins</td>
<td>-</td>
<td>-</td>
<td>• Complexation approach with Cyclodextrins (CDs) was applied for encapsulation of RIF by means of different Cyclodextrins inclusion complexes of RIF with hydroxyl propyl β cyclodextrin (HPβCD).</td>
<td>Ferreira et al., 2004; Mehta et al., 2005</td>
</tr>
<tr>
<td>RIF–β-CD and HPβCD</td>
<td>Mycobacterium tuberculosis</td>
<td>-</td>
<td>• Complexation with β-CD and HPβCD of RIF in order to improve the chemical stability and aqueous solubility of the drug and complexes showed a significant decrease in the MIC (minimum inhibitory concentration) from 64 to 32 μg/mL</td>
<td>Rao et al., 2006</td>
</tr>
<tr>
<td>Nitroimidazole P-824–HPγ-CD (Oral)</td>
<td>Mycobacterium tuberculosis</td>
<td>Mouse infection model</td>
<td>• Poorly water soluble nitroimidazole P-824 (a new anti-TB drug effect against drug-sensitive and multidrug resistant bacilli) HP-γ-CD complex showed reduction in bacterial load in the lungs at 50 and 100 mg/kg doses.</td>
<td>Lenaerts et al., 2005</td>
</tr>
</tbody>
</table>

**Solid lipid nanoparticles:** Solid lipid nanoparticles (SLNs)(Weiss et al., 2014) are colloidal particles of a lipid matrix, produced by replacing the liquid lipid (oil) of an O/W emulsion by a solid lipid or a blend of solid lipids, i.e., the lipid particle matrix being solid at both room and body temperature (Müller, 1991). SLNs were developed as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles etc. SLNs have been investigated for various pharmaceutical applications, e.g. Parenteral, Per oral, Dermal, Ocular and Pulmonary administrations. Moreover, number of routes of administration such as topical, oral, parenterals, nasal and pulmonary has been proposed for the delivery of lipid nanoparticles. Solid lipid nanoparticles entrapping lipophilic and hydrophilic/amphiphilic drug formulae were utilized for compatible in vivo degradation, possibility of controlled drug release, drug targeting and avoidance of organic solvents etc (Kaur and Bhandari, 2013). SLNs are composed of 0.1% (w/w) to 30% (w/w) solid lipid dispersed in an aqueous medium and if necessary stabilized with preferably 0.5% to 5% (w/w) surfactant. SLN can be prepared by using lipid(s), waxes and biocompatible surfactant(s) using various methods reported in the literature (Mukherjee et al., 2009). SLNs have applications in drug delivery system, cosmetics (Petit et al., 2013), clinical medicine, agriculture, biotechnology and long-term conservation of fruits, vegetables, seeds, cereals and/or fresh foodstuffs (Guerrero et al., 2014). In last two decades, SLNs have been reported as a potential carrier for chemotherapies and diagnostic applications because SLNs have several advantages (Table 7) over other colloidal carriers.

The second generation lipid nanoparticles were made by modification in the composition of solid lipid and liquid lipid to overcome the limitation associated with SLNs listed in Table 8. These second generation lipid nanoparticles are: (Mukherjee et al., 2009)
- **Nanostructured Lipid Carriers (NLCs):** Composition of solid lipid and a spatially different liquid lipid as the carrier; and
- **Lipid Drug Conjugates (LDCs):** Salt formation or covalent linkage of insoluble drug–lipid conjugate bulk with a solid matrix.

NLCs and LDCs are commonly known as solid lipid matrix with mean particle size in the submicron range, ranging from about 40 to 1000 nm. Lipid nanoparticles are the alternative carrier systems for encapsulation of antitubercular drugs are listed in Table 9.

**Future prospects:** The objective of the conventional treatment of tuberculosis (pulmonary or extrapulmonary) with anti-tubercular drugs as Directly Observed Treatment Short course (DOTS) to eradicate the causative mycobacterium infection. However, it is currently out of reach because of the difficulty in diagnosis, inconvenience in treatment, long duration, high cost of therapy along with associated side effects and emergence of multi drug resistance. It is necessary to consider the general prevention during chemotherapy, discovery of new molecules and the current situation even necessitates the re-engineering and repositioning of some old antitubercular drugs. The controlled/sustained release and targeted delivery would make it possible to reduce dosing frequency, short duration of treatment thereby improve patient compliance. The novel
nanocarrier-based drug delivery systems are in various phases of development and showed incredible promise to target the site of action, reducing the dosing frequency and enhance drug bioavailability. The future prospects of nanotechnology based treatment will improve the diagnosis and treatment, and also provide the flexibility of selecting the invasive and non-invasive route of delivery for chemotherapy of tuberculosis.

### TABLE 7
Advantages of solid lipid nanoparticles.

<table>
<thead>
<tr>
<th>Common Advantages of solid lipid nanoparticles are:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• The possibility of controlled drug release and drug targeting. (Schwarz et al., 1994; Müller et al., 2000)</td>
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<tr>
<td>• Generally less toxic as compared to some polymeric nanoparticles because physiological and biocompatible lipids are used. (Müller et al., 1996; 1997)</td>
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<tr>
<td>• Reduces the side effects like: Irritation, hypertension, toxicity etc.</td>
<td></td>
</tr>
<tr>
<td>• Reduce the dose of the drug and cost of the therapy.</td>
<td></td>
</tr>
<tr>
<td>• Large scale production and sterilization is possible. (Schwarz et al., 1994; Cavalli et al., 1997)</td>
<td></td>
</tr>
<tr>
<td>• Nano sizing enhance the permeability and easy to target.</td>
<td></td>
</tr>
<tr>
<td>• Excellent reproducibility of the product by various techniques.</td>
<td></td>
</tr>
<tr>
<td>• Protecting the labile and sensitive drugs from chemical, photochemical or oxidative degradation, due to immobilization of drug molecules by solid lipids and reduce drug leakage as commonly observed in liposomes. (Westesen et al., 1993)</td>
<td></td>
</tr>
<tr>
<td>• Low cost of solid lipids as compared to phospholipids and biodegradable polymers.</td>
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<tr>
<td>• Lipase enzyme degrades the carrier lipid and hence safe.</td>
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<tr>
<td>• Lipid carrier systems are solid at room and body temperature.</td>
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<tr>
<td>• SLNs having the particle size range of 120-200 nm are not taken up readily by the cells of the Reticulo-endothelial system and thereby bypass liver and spleen filtration.</td>
<td></td>
</tr>
<tr>
<td>• SLN have been proposed as a colloidal drug carrier therapeutic system for different administration routes such as oral, dermal, ophthalmic, pulmonary, rectal and parenteral administration. (Shaji and Jain, 2010)</td>
<td></td>
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</tbody>
</table>

### TABLE 8
Disadvantages of solid lipid nanoparticles.

<table>
<thead>
<tr>
<th>Limitations of solid lipid nanoparticles are:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>• Poor drug loading capacity.</td>
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<tr>
<td>• Drug expulsion after polymeric transition during storage.</td>
<td></td>
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<tr>
<td>• Relatively high water content of the dispersions approx. 70-99%.</td>
<td></td>
</tr>
<tr>
<td>• The low capacity to load water soluble drugs due to partitioning effects during the production process.</td>
<td></td>
</tr>
<tr>
<td>• If any damage occurs at the molecular level then it is not possible to revert.</td>
<td></td>
</tr>
<tr>
<td>• The high production manufacturing cost of nanoparticles leads in overall product cost.</td>
<td></td>
</tr>
<tr>
<td>• Can cause immune response and allergic reactions in body.</td>
<td></td>
</tr>
<tr>
<td>• Due to their small size and large surface area nanoparticles are difficult to handle in physical form because of particle-particle aggregation.</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 9
The solid lipid nanoparticles encapsulated antitubercular drugs.

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Target site/ Microorganisms</th>
<th>Exp. Model/ in vitro /in vivo Studies</th>
<th>Activity</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| RIF/ISN/ PYR (Oral/Inhalation) | *Mycobacterium tuberculosis* | Mice and Guinea pig | • Improve drug bioavailability and reducing the dosing frequency.  
• Significant improvement in the pharmacokinetic parameters. | Pandey et al., 2005a; Pandey and Khuller, 2005b; 2009 |
| RIF | *Mycobacterium fortuitum* ATCC 2701P | - | • The antimycobacterial efficacy was greatly improved against *M.fortuitum*.  
• RIF-SLNs also sustained the drug release for 72 hr. | Aboutale et al., 2012 |
| INH | *Mycobacterium tuberculosis* | *In vitro* Studies | • Improve entrapment efficiency.  
• SLN could be alternate method for prolonged drug release and better therapeutic effect. | Nair et al., 2011; Bhandari and Kaur, 2013 |
| Vitamin D3 and retinoic acid | Tuberculosis | Patent | • The nanoparticles of Vitamin D3 and retinoic acid in the present invention have the utility in treatment of tuberculosis. | Kaur and Verma, 2013 |
Conclusions

The current chemotherapy of tuberculosis dates back to the 1950s and shows poor patient compliance, poor bio-distribution, multiple side effects and drug resistance is the most common reason for the failure of chemotherapy. However, it is necessary to develop newer modalities for the treatment of mycobacterium infection. Nowadays, pharmaceutical companies have developed new drug molecules which are under various phases of clinical trials or preclinical development. These drugs showed promising activity against sensitive and resistant TB strains. Over the last few decades, the applications of nanotechnology based drug delivery have been extensively explored to overcome the failures of conventional chemotherapy and improve patient compliance. The researcher groups showed much interest worldwide in diagnoses and treatment of tuberculosis via drug loaded nanoparticles carriers because these carriers showed significantly improvement in pharmacokinetics due to high serum solubility with immense improvement of bioavailability, site targeting, sustain/controlled release, prolong systemic circulation which leads to reduction in dosing frequency.

References


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