Nanotechnology based drug delivery system(s) for the management of tuberculosis

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The era of nanotechnology has allowed new research strategies to flourish in the field of drug delivery. Nanoparticle-based drug delivery systems are suitable for targeting chronic intracellular infections such as tuberculosis. Polymeric nanoparticles employing poly lactide-co-glycolide have shown promise as far as intermittent chemotherapy in experimental tuberculosis is concerned. It has distinct advantages over the more traditional drug carriers, i.e. liposomes and microparticles. Although the experience with natural carriers, e.g. solid lipid nanoparticles and alginate nanoparticles is in its infancy, future research may rely heavily on these carrier systems. Given the options for oral as well as parenteral therapy, the very nature of the disease and its complex treatment urges one to emphasize on the oral route for controlled drug delivery. Pending the discovery of more potent antitubercular drugs, nanotechnology-based intermittent chemotherapy provides a novel and sound platform for an onslaught against tuberculosis.

Keywords: Alginate, Liposomes Nanoparticles, Poly lactide-co-glycolide, Tuberculosis.

Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis, is a major infectious burden worldwide and statistical estimates continue to worsen with each passing year (Table 1)1-5. The control of TB oscillates around a preventive arm, i.e. vaccination and a therapeutic arm, i.e. chemotherapy. Vaccination is the most desirable means of preventing TB. The reason behind the success of vaccines, in general, lies to a large extent in their ability to enable the body to respond to the invading microbes, rather than directly treating the disease with antibiotics. However, the currently available vaccine for TB, i.e. Bacillus Calmette Guerin (BCG) suffers from several demerits such as a variable efficacy in different populations, limited success against pulmonary TB that accounts for most of the disease burden and short-term immunity6. The current trend is the development of subunit vaccines by using molecular techniques for the isolation of different macromolecules of disease causing organisms. Nevertheless, it is realized that several years, if not decades, would elapse before a candidate TB vaccine could take over BCG and is precisely the reason why an improvement in the current TB-chemotherapy should be the immediate short-term goal.

It has been a long time since an effective chemotherapeutic regimen is available for TB; however, the treatment schedule poses several problems that can result in therapeutic failure. Among these problems, the foremost is the need to administer multiple antitubercular drugs (ATDs) daily that is frequently associated with patient non-compliance. Further, most of the frontline ATDs are hepatotoxic and at least in some patients they fail to eradicate persistent bacilli4. The ongoing DOTS (Directly Observed Treatment, Short course) programme has not been completely successful in solving the problem of patient non-compliance3. Most of the patients fail or are unable to adhere to multidrug therapy daily for such a longer period. Even the principal cause for the generation of drug resistant TB generally appears to be associated with low patient compliance. The

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Table 1 — Salient statistical estimates for tuberculosis1-5

- Affects one-third of the world’s population, i.e. nearly 2 billion individuals
- Responsible for 3 million deaths annually
- Most of the infections are latent with a 2-23% lifetime risk of developing reactivation TB
- India accounts for 20% of all new TB cases in the world each year
- Resistance to key frontline anti-TB drugs range from 1-10%
- The United Nations Millennium Development Goals (MDGs) for a 50% reduction in TB prevalence and deaths globally between 1990 and 2015 is a formidable task especially in endemic zones
chemotherapeutic strategies against TB include—
(i) derivatize existing ATDs into more potent
compounds; (ii) screening of compounds active
against replicating as well as latent bacilli; and (iii)
identify novel drug targets and design appropriate
inhibitors; and (iv) targeting host-pathogen related
processes essential for survival in human disease.
While the strategies are indeed worthwhile to go
ahead with, the associated drawbacks do cause
concerns—(i) involvement of intense research efforts;
(ii) difficulty in targeting latent bacilli; and (iii)
uncertainty with respect to toxicity and drug
resistance. Considering the fact that in the recent
years no new frontline ATD has been introduced, it
would be prudent and rational to develop sustained-
release drug formulations (using ATDs already in
current clinical practice) in order to reduce the dosing
frequency. We have ample experimental evidence
supporting the feasibility of this approach that is the
focus of the present review.

**Types of drug carriers**

Carriers are broadly classified as being synthetic or
natural. Poly (DL-lactide-co-glycolide) (PLG), polylactic
acid (PLA), polyglycolic acid (PGA), polyanhydrides,
polymethyl acrylates, carbomer etc. are common
examples of synthetic carriers used as drug delivery
vehicles. On the other hand, natural carriers include
lipids (liposomes and solid lipid nanoparticles),
alginic acid, chitosan, gelatin, dextrins etc. Carriers
not only help in designing different delivery system
but also provide the flexibility of selecting the route
of delivery. Thus, depending on the type of
formulation, one may attempt to deliver ATDs as
implants/injections or via the oral and respiratory
routes (Table 2). Each of the delivery modes has been
extensively evaluated in experimental TB models
(Table 3).

**Synthetic carriers for antitubercular drugs**

**Injectable microparticle based drug delivery systems**

Poly (DL-Lactide-co-glycolide) (PLG, Fig. 1) is a
copolymer of lactic acid and glycolic acid that is
completely biodegradable, biocompatible and has
been extensively used for medical procedures as well
as for encapsulating antibiotics, antigens and peptides
in order to develop sustained-release delivery
systems. We have used the 50:50 resomer of PLG
that has a half-life of 1-2 months and is appropriate
for a one-dose-after every one/two months. Rifampicin
was selected for encapsulation in PLG with the idea that rifampicin being a hydrophobic
drug, it would form strong hydrophobic interactions
with the hydrophobic PLG, thereby ensuring lesser
amount of drug being released from PLG. Three
different kinds of PLG formulations (each
encapsulating rifampicin) were developed, i.e. porous,
non-porous (based on their drug release behaviour)
and hardened (based on the use of polyvinyl alcohol,
PVA, as a hardening agent). The best results were obtained with hardened PLG microparticles (PLG-MP), which exhibited 12-14% encapsulation for rifampicin and sustained drug release for 42 days in all the organs following a single subcutaneous shot to mice. Perhaps, PVA-stabilized PLG-MP effectively formed a depot at the injection site resulting in the subsequent controlled drug release. When isoniazid was substituted for rifampicin, the drug could be detected in the organs till day 49 (Ref. 11). The biodistribution and therapeutic efficacy of PLG-MP encapsulated rifampicin and isoniazid (alone or in combination) given as a single subcutaneous injection to mice was evaluated12,13. It was observed that therapeutic drug levels were maintained in the organs upto 6 weeks. Further, PLG-MP exhibited a better/equivalent bacterial clearance compared to free drugs administered daily. Gangadhar et al14 have also documented the effectiveness of microsphere technology for tuberculosis. However, these systems involved implants as the mode of drug delivery which has practical limitations such as the need for surgical manoeuvres and the risk of toxicity of N-methyl pyrrolidine used in the preparation process. Hence, injectable systems would be preferred to implantable ones as far as the application of parenteral ATD delivery is concerned.

**Oral microparticle based drug delivery systems**

Although encouraging results were obtained with PLG-MP administered as a single subcutaneous injection, the pain and discomfort associated with the latter led us to formulate an oral drug delivery system with PLG-MP. We also included pyrazinamide, another frontline ATD, in our therapeutic regimen. A sustained drug release for 3-5 days was observed in plasma after a single oral administration of PLG-MP encapsulated drugs to mice. The PLG-MP, because of their bioadhesive nature, maintains contact with the intestinal mucosa for an extended period of time before they are absorbed or release their contents. This was the first report15 of PLG as a vehicle for ATD by the oral route and it predicted a once-weekly oral treatment for TB. The evaluation of once weekly regimen for 6 weeks with PLG-MP indeed demonstrated a significant reduction in bacterial counts in *M. tuberculosis* infected mice16. Similar findings were reported by other eminent scientists in the field of microsphere technology17,18.

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PANDEY & KHULLER: NANOTECHNOLOGY BASED DRUG DELIVERY SYSTEM

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UR – unpublished data
Inhalable microparticle based drug delivery systems

Pulmonary TB being the commonest form of the disease, the respiratory delivery of ATDs is an attractive proposition. The microspheres were administered via insufflation or nebulization to guinea pigs, 24 h prior to aerosol infection with *M. tuberculosis* H37Rv. The model was adopted as a post treatment screening method for antimicrobial efficacy. The assessment of cfu 28 days post infection showed a dose-effect relationship, i.e. lower cfu with higher doses of microspheres. The cfu count was significantly reduced compared with free rifampicin. With a similar experimental approach, the authors next evaluated the effect of repeated dosing of rifampicin. With a similar experimental approach, the microspheres were administered at every 10th day. At 10 days post infection, half of the treatment group received a second dose of the microspheres. There was a significant reduction in cfu in lungs (but not in spleens) in case of animals receiving a single dose of the formulation whereas 2 doses resulted in a significant decrease in cfu in lungs as well as in spleens. Other investigators encapsulated isoniazid with rifampicin in poly lactide microparticles for dry powder inhalation to rats. Drug concentrations inside the alveolar macrophages were found to be higher than that resulting from vascular delivery of free drugs, an indication of the rapid phagocytic uptake and cytosolic localization of the drug-loaded microparticles. In order to reduce the drug dosage, investigators have also formulated an inhalable microparticulate system for para aminosalicylic acid (a second line ATD) based on dipalmitoylglycerol-3-phosphocholine.

Nanotechnology and tuberculosis

The applications of nanotechnology 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. 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. Mononuclear phagocytes, dendritic cells, endothelial cells and cancers cells are the key targets as far as nanotechnology based drug delivery is 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. Nanoparticles are 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. 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, solvent displacement/nanoprecipitation, emulsion-diffusion, emulsification-solvent displacement/nanoprecipitation, emulsion-diffusion-emulsification etc.

Oral nanoparticle based drug delivery systems

With our main research interest focused on mycobacteriology, we tested the feasibility of using ATDs in nanoparticle based controlled delivery devices. Three frontline ATDs, i.e. rifampicin, isoniazid and pyrazinamide were co-encapsulated PLG nanoparticles (PLG-NP), prepared by the double emulsion and solvent evaporation technique. The particle size ranged from 186-290 nm with a drug encapsulation efficiency of 60-70% for all the drugs. Particle size distribution homogeneity was indicated by a polydispersity index of 0.38. The formulation was evaluated for its in vivo pharmacokinetic and pharmacodynamic potential at therapeutic drug doses, i.e. rifampicin 12 mg/kg + isoniazid 10 mg/kg + pyrazinamide 25 mg/kg body weight. Following a single oral administration of drug loaded PLG-NP to mice, the plasma drug levels were maintained above their minimum inhibitory concentration (MIC90) for 6-9 days in the plasma and in organs (lungs, liver and spleen) for up to day 9. However, free drugs were cleared from the plasma and organs within 12-24 h of oral administration. It was also demonstrated that oral dosing with the PLG formulation at every 10th day did not result in progressive drug accumulation in the
The chemotherapeutic evaluation of free drugs administered daily (46 doses) and drug-loaded PLG-nanoparticles administered every 10 days (5 doses) orally to \textit{M. tuberculosis} infected mice, showed no detectable tubercle bacilli compared with a bacterial load of nearly 4.8 log cfu in lungs/spleen of untreated mice\textsuperscript{33}. Similar findings were observed in a higher animal model, i.e. guinea pigs\textsuperscript{34}.

The WHO recommends the addition of the bacteriostatic drug ethambutol, to the intensive phase of chemotherapy. Hence, the chemotherapeutic potential of PLG-nanoparticle encapsulated ethambutol, when co-administered with the other 3 encapsulated frontline ATDs, was evaluated. Following a single oral therapeutic dose of ATD-loaded PLG nanoparticles to mice, the MIC levels were maintained in the plasma for 3, 6 and 8 days in case of ethambutol, rifampicin and isoniazid/pyrazinamide respectively. In the tissues, RIF, isoniazid and pyrazinamide were detected till day 9 as previously reported\textsuperscript{33}, while ethambutol was maintained till day 7. Free drugs, on the other hand, were not detectable in the plasma beyond 12 h and in the tissues beyond 24-48 h of oral administration. Hence, the ATD-loaded PLG nanoparticles were administered to \textit{M. tuberculosis} infected mice at every 10\textsuperscript{th} day, while free drugs were administered daily. There was a significant reduction in bacterial load in the 3-drug combination treated groups at 4 weeks post-chemotherapy. However, there were no detectable cfu (<1.0) in those groups where ethambutol was supplemented to the 3-drug regimen, demonstrating the potential of the 4-drug combination to shorten the duration of treatment\textsuperscript{35}. Thus, with the 4-drug combination in PLG nanoparticles, it was possible to improve the drug bioavailability, to reduce the dosing frequency and to reduce the number of drug doses. Potential mode of entry of PLG-nanoparticles can be through M cells, normal epithelial cells or by paracellular route. Though particles in nano-range have been shown to use a transcellular or paracellular route. However number of reports demonstrate their uptake via membrane epithelial cells\textsuperscript{36}.

Nanoparticles can be also targeted to specific sites by tagging them with suitable ligands. Attempts have been made to make PLG-nanoparticle uptake more effective by functionalizing them with various lectins\textsuperscript{37}. The nanoparticulate system was further improved by the addition of lectin, a mucosal ligand, to the PLG nanoparticles. Wheat germ agglutinin (WGA) is a commonly occurring plant lectin having low immunogenicity. The receptors for WGA are distributed on intestinal/respiratory epithelium, thus favoring its use for oral as well as aerosol drug delivery. The sustained release profile and pharmacokinetics of all the ATDs was improved significantly as the drugs were detectable in the tissues till day 15 in case of the lectin coated formulation against day 11 in case of the uncoated formulation. In \textit{M. tuberculosis} H\textsubscript{37}Rv infected guinea pigs, 3 oral doses of ATD loaded lectin PLG-NP spaced 15 days apart resulted in undetectable cfu against 46 conventional doses of oral free drugs\textsuperscript{36}.

The efficacy of the PLG-formulation was also assessed in animals infected via the aerosol route because the latter is the natural mode of acquiring TB. In guinea pigs infected via the aerosol route, 5 oral doses of ATD loaded PLG-NP and 46 doses of free drugs still proved to be equiefficacious\textsuperscript{38}. This further strengthened the concept of controlled release ATD delivery systems.

**Inhalable nanoparticle based drug delivery systems**

Inhalable nanoparticles stand better chances of mucosal adherence, particle(s) delivery and hence net drug delivery to the lungs\textsuperscript{39}. PLG nanoparticles co-encapsulating rifampicin, isoniazid and pyrazinamide were administered by the aerosol route to guinea pigs. Upon aerosolization, the mass median aerodynamic diameter (MMAD) was found to be 1.88 $\mu$m suitable for deep lung delivery. A single nebulization of the formulation to guinea pigs was able to maintain therapeutic drug concentration in the plasma for 6-9 days and in the lungs for 9-11 days. There was a significant improvement in the half-life, mean residence time and relative/absolute bioavailability of encapsulated drugs compared with free drugs\textsuperscript{40}. Repeated administration of the formulation failed to elicit hepatotoxicity as assessed on biochemical basis. In \textit{M. tuberculosis} H\textsubscript{37}Rv infected guinea pigs, 5 nebulized doses of the formulation spaced 10 days apart, resulted in undetectable cfu in the lungs replacing 46 conventional doses. This was the first report of PLG nanoparticles as an inhalable ATD carrier\textsuperscript{40}. The advantage of the system over inhalable microspheres was clear-cut; firstly, it was possible to co-administer three ATDs encapsulated in nanoparticles\textsuperscript{40} whereas, respiratory delivery with microparticles was restricted to one\textsuperscript{20,21} or two\textsuperscript{22} drugs; and secondly, the reduction in mycobacterial load in the lungs was better in case of respirable
nanoparticles\textsuperscript{40} compared with microparticles\textsuperscript{20,21}. Further, upon nebulization of lectin-functionalized PLG nanoparticles to guinea pigs, therapeutic drug concentrations were maintained in the plasma for 6-10 days and in the organs for 15 days. Most of the pharmacokinetic parameters were enhanced compared with uncoated PLG nanoparticles and free drugs. Most importantly, when nebulized to TB-infected guinea pigs every fortnightly, 3 doses of the formulation produced undetectable cfu in the lungs as well as spleens\textsuperscript{37}. The series of experiments proved that 46 conventional doses could be reduced to 5 nebulized doses of PLG nanoparticles and further to just 3 doses with lectin-PLG nanoparticles.

**Injectable nanoparticle based drug delivery systems**

The subcutaneous and intramuscular routes provide bioavailability profiles close to the intravenous route. An important attribute of PLG nanoparticles was a high chemotherapeutic efficacy following subcutaneous administration\textsuperscript{41}. 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\textsuperscript{42,43}. 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\textsuperscript{42}. They have been approved by FDA, USA for human use through subcutaneous route\textsuperscript{44}. A long term depot delivery system of an LH-RH superagonist, leuproretin acetate is currently available in the third market\textsuperscript{45}. These observations thus further support the application of PLG-based nanotechnology for mycobacterial infections.

**Natural carriers for antitubercular drugs**

**Liposome-based drug delivery systems**

Liposomes consist of a lipid shell surrounding an aqueous core (Fig. 2). The advantage of using liposomes is that they are avidly taken up by alveolar macrophages (the abode of \textit{M. tuberculosis}), release their contents (e.g. drugs) intracellularly and are effective against intracellular pathogens\textsuperscript{46}. Since, liposomes are vulnerable to intestinal lipases, they need to be administered by the intravenous route. We have previously reported that liposomes can be selectively targeted towards the lung tissue by specifically tagging them with o-stearyl amylopectin\textsuperscript{47}. Non-specific uptake by the reticuloendothelial system of liver and spleen can be reduced by the inclusion of polyethylene glycol in the liposomal formulation\textsuperscript{47,48}. Such lung specific stealth liposomes have been shown to be stable and slowly release the encapsulated ATD. On administration to \textit{M. tuberculosis} infected mice twice a week for 6 weeks, liposome encapsulated drugs (rifampicin or isoniazid alone) were more effective in clearing mycobacterial infection than free drugs\textsuperscript{47}. However, when the above two frontline ATD were co-administered in liposomes, the therapeutic schedule was successfully reduced to once weekly administration for 6 weeks. Further, the drug dosage was curtailed to 1/3\textsuperscript{rd} of their therapeutic doses\textsuperscript{49}. No hepatotoxicity was produced as assessed by histopathological examination and supported by serum bilirubin, alanine aminotransferase as well as alkaline phosphatase\textsuperscript{50}.

Liposomes offer the possibility of nebulization and administration via the respiratory route for selective targeting to alveolar macrophages\textsuperscript{51,52}. We have demonstrated the feasibility of nebulizing liposome
encapsulated ATD to guinea pigs. It has been observed that rifampicin/isoniazid remain in the circulation for 24-48 h, whereas, alveolar macrophages recovered from the bronchoalveolar lavage of guinea pigs were found to contain rifampicin/isoniazid till day 5 post-nebulization. These findings suggest that daily oral dosing may be reduced to one dose every 5-7 days by aerosolized liposomes in infected guinea pigs to achieve therapeutic benefits. Our findings were supported by the results of Kurunov et al. who reported an equivalent therapeutic efficacy of twice weekly-nebulized liposomal rifampicin and daily conventional rifampicin in a murine TB model. It was suggested that liposomal formulation helps in the persistence of rifampicin in lungs. Ligand appended inhalable liposomes entrapping rifampicin were demonstrated to achieve a higher pulmonary delivery and better localization to alveolar macrophages in rats compared with conventional liposomes or free rifampicin. Therefore, nebulization of liposomal ATDs, coupled to the use of alveolar macrophage specific ligands, may be a useful adjunct to conventional chemotherapy of pulmonary TB. The safety of inhaled liposomes also favors its use via the respiratory route.

**Solid lipid nanoparticle based drug delivery systems**

The degradation of liposomes by intestinal lipases prohibits their use via the oral route. Solid lipid nanoparticles (SLNs) are nanocrystalline suspensions in water (prepared from lipids that are solid at room temperature) and can be administered orally. The SLNs possess good tolerability (being derived from physiological lipids), scaling-up feasibility, the ability to incorporate hydrophobic/hydrophilic drugs and an enhanced stability of incorporated drugs. Thus, SLNs are unique in the sense that they combine the virtues of traditional nanoparticles while eliminating some of their demerits. The ATD-loaded SLNs were prepared by the emulsion solvent diffusion technique to co-incorporate rifampicin, isoniazid and pyrazinamide. The chemotherapeutic potential of the formulation was evaluated via the respiratory route in guinea pigs. It was observed that a sustained drug release was maintained for 5 days in plasma and for 7 days in the organs. The pharmacokinetics was unaltered in healthy as well as TB infected guinea pigs. Seven weekly doses of the formulation resulted in undetectable bacilli in the organs of TB infected guinea pigs, replacing 46 conventional doses. This was the first report of the chemotherapeutic efficacy of SLNs in experimental TB. Next, the studies were carried out via the oral route and better results were obtained as the drug levels could be maintained in the plasma for 8 days and in the organs for 9-10 days. Five oral doses of the formulation spaced 10 days apart were as efficacious as 46 doses of oral free drugs in terms of producing bacterial clearance in TB-infected mice.

**Alginate based drug delivery systems**

Alginate is a natural co-polymer of guluronic acid and mannuronic acid (Fig. 3). Alginate is already in clinical use for the supportive treatment for reflux esophagitis. It has found applications as a binding and disintegrating agent in tablets, a suspending and thickening agent in water-miscible gels/lotions/
creams and as a stabilizer for emulsions. Several attributes make alginate an ideal drug delivery vehicle. These include – (i) a relatively high aqueous environment within the matrix; (ii) adhesive interactions with intestinal epithelium; (iii) a mild room temperature drug(s) encapsulation process free of organic solvents; (iv) a high gel porosity allowing high diffusion rates of macromolecules; (v) the ability to control this porosity with simple coating procedures using polycations; and (vi) biodegradation of the system under physiological conditions. Hence, it is not surprising that alginate has been used as a carrier for the controlled release of antibiotics including ATDs. Following the encapsulation of RIF, INH and PZA in alginate microspheres and oral administration to guinea pigs, therapeutic drug concentrations could be maintained in plasma for 4-5 days and in organs for 7-9 days. Weekly treatment with the formulation resulted in complete bacterial clearance in organs of infected guinea pigs after 8 oral doses, as did the daily oral administration of free drugs. A few refinements in the methodology with the inclusion of chitosan, resulted in a system which was better than the simple alginate system in terms of drug encapsulation/loading, pharmacokinetics and chemotherapeutic efficacy. The most important observation was the ability of the alginate-chitosan system to document a therapeutic benefit with just half therapeutic dose administered weekly. Further, alginate-chitosan nanoparticles have also been developed in which the consumption of polymers has further been reduced besides maintaining the advantages of nanoparticles. The formulation, which uses 7.5-fold less amount of polymer compared with the alginate formulations discussed above, can be administered by the oral route or nebulized. A single oral administration of the formulation could maintain therapeutic drug concentrations in the plasma/organs of mice/guinea pigs for 2 weeks (unpublished data). An almost similar profile was obtained by the aerosol route in guinea pigs. There was a total clearance of bacilli following 6 weeks of chemotherapy comprising of 3 nebulized doses of the formulation.

Future perspectives

Several synthetic/natural carrier-based controlled release formulations encapsulating key first line ATDs have been explored out of which the nanoparticles appear to be the best in terms of therapeutic efficacy (Fig. 4). Further, practical considerations dictate that the oral route would be the preferred one for drug delivery. Most of the preclinical studies have been completed with oral PLG nanoparticles and future work should emphasize on this platform technology to develop the formulation on a large-scale at an affordable cost. Studies with alginate nanoparticles, though encouraging, but still requires further investigations. Suitably designed clinical studies should bring out the final answer to whether nanoparticle based drug delivery systems might be the long-sought solution for improving the patient compliance in TB chemotherapy.

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