Nanotechnology: Its Usages in Drug Delivery for the Treatment of Human Parasitic Diseases

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Abstract

The occurrence of infectious parasitic disease is the leading driver of mortality worldwide. Treatment of such parasitic disease is challenging due to the minimal target bioavailability of antiparasitic drugs, poor cellular uptake, nonspecific distribution at the target site and rapid elimination from the body. Further antiparasitic drug toxicity and prolonged therapeutic regimens also concerns us. Leading trends in nanotechnology can overpower these shortcomings in the form of an ideal nanocarrier system that can be designed and fabricated accordingly, where new formulations and the existing antiparasitic drugs in nano-sized delivery vehicle can be more promising in terms of minimized non-specific drug accumulation, desired antiparasitic drug availability at the site of action, reduced therapeutic dose and duration that is to be delivered etc. Through this chapter, we have highlighted the major challenges of conventional treatment approaches and presented nanotechnology as an imminent alternative treatment approach for the infectious parasitic disease. However, the unification of these two-research areas as "nano-antiparasitic medicines" can progress as a therapeutic strategic plan, minimising the burden of individuals suffering from this worldwide.

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A. Singh et al. (eds.), *Natural Product Based Drug Discovery Against Human Parasites*, https://doi.org/10.1007/978-981-19-9605-4_9

Keywords

Nano carrier · Antiparasitic drugs · Nano-antiparasitic medicines · Therapeutic regimens

Abbreviations

AmB	Amphotericin B
Aphi	Aphidicolin
Ber	Berberine
CR	Curcumin
Lip	Liposomes
NE	Nano emulsion
NLCs	Solid lipid nanoparticles
NPs	Nanoparticles
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PLGA	Poly(lactic-*co*-glycolic acid)
PZQ	Praziquantel

9.1 Introduction

Infectious parasitic diseases are of major concern to public health worldwide. Their occurrence and pathological prevalence are closely related to geographic and socio-economic factors (Cable et al. 2017). However, in India, their pervasiveness is determined by climate change, as such changes turn on favorable condition for the spread of vectorborne infectious parasitic diseases, it accounts for 17% of all infectious diseases. The most common vector-borne infectious parasitic diseases are visceral leishmaniasis, malaria, dengue, chikungunya, Japanese encephalitis, lymphatic filariasis etc. (Leal Filho et al. 2022). Further, the causative agent (pathogen) for infectious parasitic diseases is usually known as parasites. These are broadly been classified as eukaryotic organisms ranging from single cellular protozoans, to large multicellular helminths responsible for severe disease onset in both animals and the human population. The various class of parasites that cause disease in the human population are protozoans, helminths, ectoparasites etc. Amongst protozoans there is subdivision based on their mode of movement this includes Sarcodina (*Entamoeba*); Mastigophora (*Giardia* and *Leishmania*); Ciliophora (*Balantidium*); Sporozoa (*Plasmodium, Cryptosporidium*). Similarly, sub division inhelminths is based on their shape this includes platyhelminths (Trematodes (flukes) and Cestodes (tapeworms)); acanthocephalins (worms reside in the gastrointestinal tract); nematodes (worms reside in the gastrointestinal tract, blood, lymphatic system or subcutaneous tissues). Under protozoan parasites severe health illness in human is

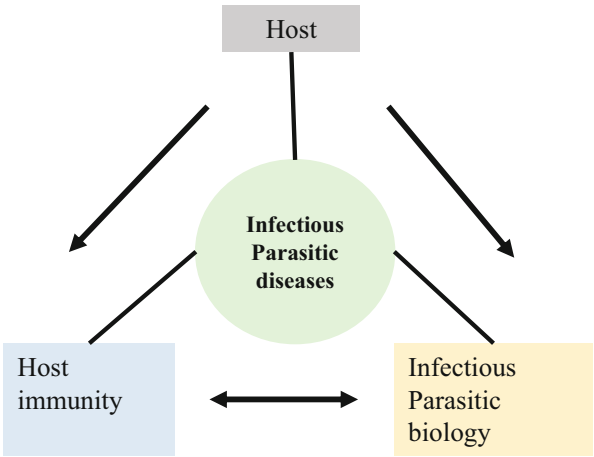

Fig. 9.1 Schematic representation of host parasite interaction

majorly caused by genus *plasmodium, entamoeba*, *acanthamoeba, leishmania, trypanosoma* and *toxoplasma* (David Sibley 2011). While for helminths the human health complications are mainly related to genus of *ascaris, schistosoma* and *tenia* (Jiménez et al. 2016). For host-parasite interaction (Fig. 9.1).

The conventional treatment approach for controlling infectious parasitic diseases is dependent on the currently available antiparasitic drugs. Major issues with the conventional treatment approach are due to its insoluble nature, shorter half-life, and minimized bioavailability of antiparasitic drugs to the target site. However, for enhanced effective therapeutic response frequent long-term booster dosage is required based on parasitic life cycles. Such treatment repetitions might introduce deleterious consequences such as stress, drug resistance, etc. (Vercruysse et al. 2007).

To overcome such limitations there is a prerequisite need for novel therapeutic approaches in the form of nanotechnology, integration of nanotechnology with parasitic disease management can design and fabricate nanomedicines with nanoparticles ranging from 1 to 1000 nm. It can have a substantial impact on parasitic diseases and its presence can aim for enhancing the efficacy of antiparasitic drugs at the target site. There are various types of nanomaterials such as organic nanocarriers that are made from desired synthetic or natural polymers, cholesterol, phospholipids, solid lipids etc. They can be designed in the form of nanospheres, nanoparticles, micelles etc. Other than this inorganic nanocarriers like metallic and non-metallic nanoparticles are also used (Sun et al. 2019). The loading of antiparasitic drugs into the nanocarrier system is a physical or chemical reactive event which occurs through adsorption, encapsulation and conjugation process. Further, its release at the target site can be a sequential event that might occur through desorption, dissolution or degradation of antiparasitic drug from nanocarrier system. These nanocarriers can easily infiltrate into the biological system where it can shield the antiparasitic drug from enzymatic degradation causing sustainable, controlled release and accumulation of antiparasitic drugs at target site etc. (Negi

et al. 2013; Das and Chaudhury 2011; Chen et al. 2015). However, effectiveness of therapeutic approach dose not completely depend on type of nanocarrier system and the properties of drug it also depends on the route of administration etc. (Chen et al. 2015, 2017). At present, nanoparticles that have been explored so far exhibit the forthcoming potential for development of "nano-antiparasitic medicines" further it also highlights its other broad developmental aspects of antiparasitic drug delivery application.

9.2 Nanoparticles Physiochemical Characteristics and Its Effect on Activity of Antiparasitic Drugs

The physico-chemical characteristics of nanoparticles has an effect on the activity of antiparasitic drugs. Enhanced efficacy of antiparasitic drugs is also dependent on the size of nanoparticle as it plays crucial role in transportation of antiparasitic drugs and distribution in an in vivo system. Thus, can be assumed to have diverse inhibitory effect on parasites. Work led by Liu and colleagues have determined that variation in the size of radiolabelled liposomes will alter the distribution in an in vivo mouse model, where in the bloodpost 4 h treatment 60% of liposomes in the size range of 100–200 nm were identified and small size nanoparticles were easily eliminated through excretion. Antileishmanial effects of gold nanoparticles of smaller size was also reported in an in vitro system (Liu et al. 1992; Want et al. 2021). Hence, selection of an appropriate size can be promising for longer retention and sustained targeted distribution of antiparasitic drugs. Therefore, optimization of the nanoparticles based on the shape and size can enhance the cellular entrance ability thus, can be promising for treating intracellular parasitic infections. Similarly, surface charges can also have an effect on the activity of antiparasitic drugs. Surface hydrophilicity or hydrophobicity can influence the kinetics in an in vivo system, its impact on protein binding extents will enable easier attaining of the estimated distribution and kinetics, modification with a desired polymer like polyethylene glycol (PEG) will increase nanoparticles surface hydrophilicity. It can significantly prolong the residence time, half-life and bioavailability of antiparasitic-loaded nanoparticles (Kumar et al. 2017; Pensel et al. 2015; Fülöp et al. 2018). Therefore, such modification of nanoparticles can be an important parameter for satisfactory sustained-release antiparasitic drugs (Fig. 9.2).

9.3 Nano-Assisted Therapeutic Regime for Parasitic Disease

Current advancements and innovations in the nanotechnology field have been extensively studied in parasitic diseases, to overcome the several frailties associated with conventional diagnosis and therapeutics. As such, anti-parasitic drug delivery systems gained attention to ameliorate their bioavailability, controlled release and intracellular penetration activity. Therefore, drug-loaded nanoparticles hold significant promise to enhance efficacy and reduce the dose and side effects of drugs. This

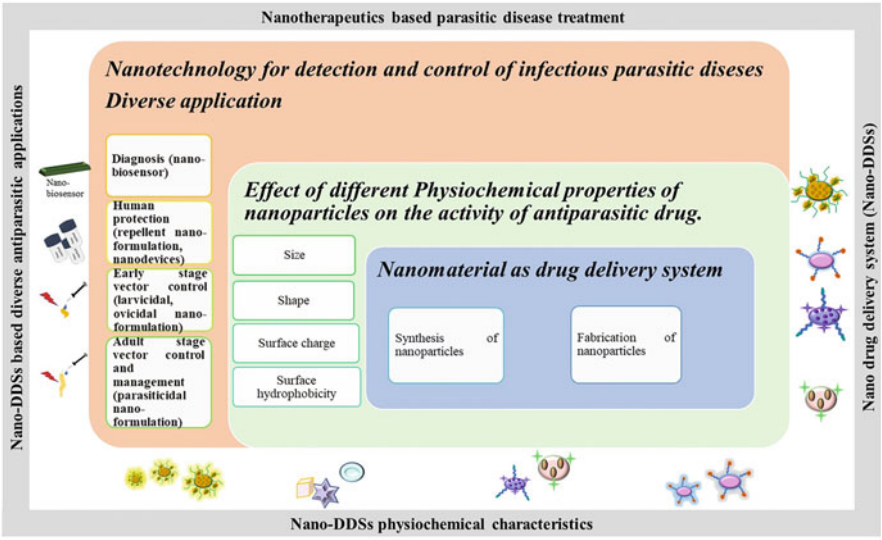

Fig. 9.2 Schematic representation of the effect of nanoparticles physiochemical properties on the activity of anti-parasitic drugs

section focuses on a variety of nanoparticles enlisted in Table 9.1 used in drug delivery systems and therapeutics diagnostics include liposomes, polymeric nanoparticles, SLNs, nanosuspensions, metallic nanoparticles and others (Fig. 9.3).

9.3.1 Liposomes

Liposomes are small artificial vesicle consisting of two or more lipid bilayer, which immobilized the drugs in bilayer or inner core when employed as a nano-carrier system, facilitates the targeted, controlled release of drug with decreased cytotoxicity. Currently, Calvo et al. constructed berberine (ber) loaded liposomes against *Leishmania infantum* infected Balb/c mice. This study demonstrated that Ber-loaded liposomes exhibited higher biocompatibility by increasing its selective index more than sevenfold in macrophages as confirmed by in vitro cytotoxicity assay and reduced parasitic burden in liver and spleen when compared to free drugs (Calvo et al. 2020; Frezza et al. 2013). The evaluation of praziquantel loaded liposomes (Lip-PZQ) on *Schistosomiasis mansoni* (BH strain) showed the following dose for 45 days to mice model decreased the parasitic egg counts and worm in intestine and liver as compared to free drugs. Therefore, this formulation enhanced the bioavailability in host organisms via targeted delivered to liver site where it is absorbed by the tegument of *S. mansoni* (Frezza et al. 2013). Additionally, Voak et al. studied the biodistribution and pharmacodynamics of Amphotericin B encapsulated liposome nanoparticles (AmBisome) at different stages of *Visceral leishmaniasis* infected Balb/c mice. It has been reported that a higher dose (10 mg/kg) of AmBisome

Table 9.1 Tabular representation of different nanoparasitic formulations studied in different parasitic diseases

Nanoparticles	Modification	Drugs	Parasite	Experimental model	Inference	References
Niosomes	–	Praziquantel (PZQ)	*Schistosoma mansoni*	*Biomphalaria alexandrina* snail host and mice infected with *S. mansoni*	PZQ-encapsulated noisome are capable of successfully overcoming the tolerance of *S. mansoni* to PZQ in mice infected with cercaria with decreased sensitivity to PZQ	Amer et al. (2022)
Liposomes	*p*-Aminophenyl-α-D-Mannopyranoside	Andrographolide	*Leishmania donovani*	Hamster Balb/c peritoneal macrophages	Targeted drug delivery to phagocytic macrophage, were found to be most effective in lowering the parasites load in the spleen as well as in lowering the hepatic and renal toxicity	Sinha et al. (2000)
Nano-emulsion	–	Curcumin	*Toxoplasma gondii*	Acute and chronic toxoplasmosis infected Balb/c mice	CR-NE possessed the enhanced anti-toxoplasma activity in both acute and chronic phase, by eliminating the latent bradyzoites in the brain	Azami et al. (2018)
Solid lipid nanoparticles	Heparin	Chloroquine	*Plasmodium falciparum*	Chloroquine-sensitive (CQS) D6 and chloroquine-resistant (CQR) W2 strains	Collaborative effect of CQ-loaded heparinized solid lipid nanoparticles (Hep-SLN), meaning that combining heparin and CQ in solid lipid nanoparticles has useful	Muga et al. (2018)

					effects, including potential for specific targeting of parasitized red blood cells as afforded by heparin by killing 50% of population	
Gold nanoparticles	Glucose	Ciprofloxacin	*Plasmodium falciparum*	Asynchronous intracellular *Plasmodium falciparum* and asexual stages of *Plasmodium falciparum* in blood	Ciprofloxacin-loaded nanoparticles rendered the moderate antimalarial drug more water-soluble, enhanced its effectiveness against *Plasmodium falciparum* through a combined effect of selective targeting, leading to accumulation of drug on the parasite, combined with better hydrophilicity to prevent the formation of drug masses	Varela-Aramburu et al. (2020)
Chitosan–gold nanoparticles	Protein-A	–	Cystic Echinococcosis	Immuno-dot-blot assay (biosensor)	This biosensor signal intensity was proportional to the amount of active anti-*Echinococcus granulosus* antibodies present on the surface of nanoparticles, antibodies titre in the sera samples, and amount of Ag B	Safarpour et al. (2021)

(continued)

Table 9.1 (continued)

Nanoparticles	Modification	Drugs	Parasite	Experimental model	Inference	References
					coated on the nitrocellulose membrane	
Gelatin	Mannose	Amphotericin B	*Visceral leishmania*	J774A.1 macrophage cells	AmB loaded f-GNPs exhibited remarkable anti-leishmanial activity and promising carrier for specific delivery of AmB to macrophages for effective treatment of VL	Nahar et al. (2010)
Copper oxide		Albendazole	*Setaria cervi*	Filarial parasite *Setaria cervi*	CuO NPs as a effective adjuvant with ABZ against filariasis along with increased antifilarial activity of nanocomposite under the UV light by increased ROS production and decrease of parasitic-GST and GSH levels were detected and as well DNA fragmentation	Zafar et al. (2016)
Poly-DL-lactic-*co*-glycolic acid (PLGA)	Chitosan	Albendazole sulfoxide	*Echinococcus granulosus*	Cystic echinococcosis infected mice	ABZ-SO-loaded CS-PGLA NPs therapeutic effect of ABZ-SO-loaded CS-PGLA NPs in the weight and volume of cysts were statistically significant when	Darvishi et al. (2020)

					compared with that in the control group ($p < 0.05$)	
Polymer nanoparticles (polycaprolactone)		Amphotericin B	*Leishmania tropica* KWH23 and *Leishmania donovani*	Leishmania infected macrophages	Anti-leishmanial activity of Amp B was significantly enhanced by macrophage targeting through drug-loaded formulations for the inhibition of intracellular parasites. Maximum parasite inhibition was provided by prepared drug-loaded formulation for anti-leishmanial activity against infected macrophages	Saqib et al. (2020)

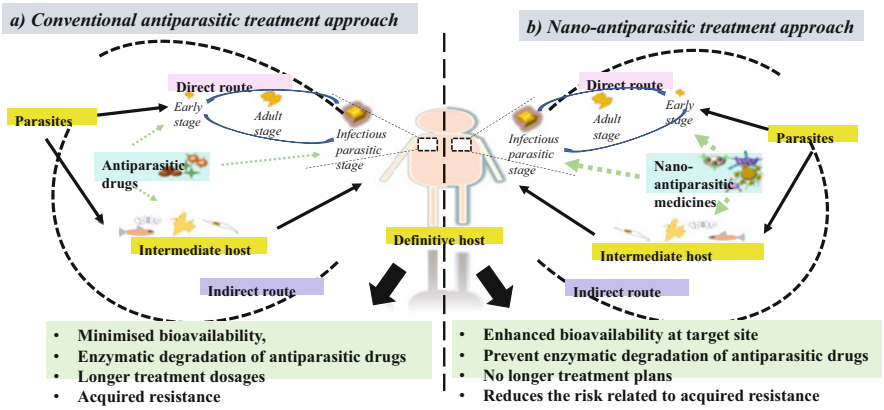

Fig. 9.3 Schematic representation of (**a**) conventional antiparasitic treatment approach, (**b**) nano-antiparasitic treatment approach [line in green color show effectiveness of anti-parasitic drugs while the line in green color with increased width shows enhance effectiveness due to the existence of nanocarriers as a drug transfer system for antiparasitic drugs distribution to target site]

kills parasite within the 48 h of 14 days of infection while drug potency was decreased when administered after 35 days of advanced infection. Drug accumulation distribution was found to be lower in spleen and liver on 35 days when compared to 14 days. This finding suggested that organ enlargement and other physiological factors are responsible for the distribution and potency of single dose of AmBisome (Voak et al. 2017). Moreover, Khodabandeh et al. demonstrated combinatorial therapy against resistant visceral leishmaniasis on 2-year-old boy. The patient was given treatment with liposomal amphotericin B, allopurinol and interferon gamma for 3 weeks. So, therefore together this treatment accelerated the complete cure. This study further suggested to identify resistant species of leishmania along with their response to different treatment (Khodabandeh et al. 2019).

Apart from other, liposomes play a lead role in providing specific and controlled distribution, toxicity reduction, prolonged circulation and minimize side effects of anti-parasitic drugs. Their potency is further increased through modification of the surface by coating with suitable moieties.

9.3.2 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are solid core lipid nonvehicle rapidly developed in current years. Mainly it is based on synthetic or natural lipids as a platform to endow drugs adsorption and encapsulation. The SLNs consolidate the advantages of conventional colloidal nano-carriers such as liposomes, oil-in-water emulsions and polymer nanoparticles, i.e., facile mass productions, highly compatible and degradable at physiological conditions. Currently, Khosravi et al. synthesized mannosylated functionalized solid-lipid nanoparticles loaded with paromomycin

(PM-SLN-M) to combat acute toxoplasmosis. Although PM has high killing rate of intracellular *Toxoplasma* in low amount in comparison to PM-SLN-M but it possessed low cytotoxicity on Vero cells. This study suggested that PM-SLN-M exhibited remarkable activity against Toxoplasma without harming the cells of the host (Khosravi et al. 2020). 5-Hydroxy-3methyl-5-phenyl-pyrazoline-1-(*S*-benzyl dithiocarbazate) (H2bdtc) loaded solid lipid nanoparticles (H2bdtcSLNs) to target *Trypanosoma cruzi*. Comparative study of benznidazole and H2bdtc-SLNs from in vitro and in vivo outcomes revealed that H2bdtc-SLNs mediate the parasitaemia reduction in mice compared to benznidazole. This study concluded that H2bdtc-SLNs formulation prevent inflammation and lesion in the liver and heart, which enhanced overall survivability in *T. cruzi* infected mice (Carneiro et al. 2014). Moreover, Radwan et al. prepared formulation of praziquantel solid lipid nanoparticles (SLN-PZQ) against murine *S. mansoni* infection. The SLN-PZQ demonstrated superior anti-schistosomal activity along with significant bioavailability and sustained release of drug in advanced *Schistosoma mansoni*-infected groups were showed remarkable inhibition and reduction of worm population in both hepatic and intestinal tissue in comparison to free PZQ (Radwan et al. 2019).

In brief, the anti-parasitic activity has not been predominately studied. Therefore, SLNs offers promising substitute besides some other nanoparticles by facilitated the sustained drug release and specific targeting.

9.3.3 Nanosuspensions

Nanosuspensions are defined by very fine submicron-dispersed colloid of solid drug nanoparticles stabilized by surfactants in aqueous medium. The potential advantages of nanosuspension offer efficient solubility, absorption, dissolution percentage and rate of drugs as well as mediates the prolonged release and reduces the systematic toxicity of drugs. It is an ideal operation to use nanosuspension apart from conventional dosage due to its affordable cost, high loading capacity, facile production and negligible adverse effects. In a study, Kayser prepared aphidicolin-loaded nanosuspensions (Aphi-loaded NSs) against leishmania-infected macrophages. This finding suggested that Aphi-loaded NSs easily phagocytosis by murine macrophage via passive target and enhanced the anti-leishmania activity approx. 140 times. This indicated that nanosuspension increased the payload of drugs and augment the sustained release of drugs to the infected site (Kayser 2000). Recently, curcumin-nanoemulsion (CR-NE) was synthesized to treat acute and chronic toxoplasmosis in mice. This study revealed that CR-NE possessed the significant anti-toxoplasmosis by inhibiting the growth of tachyzoites in Peritoneum were observed in both acute and chronic phase compared to curcumin (CR). In addition, decreased in cyst count were determined by the downregulation of BAG1 were maximum in CR-NE treated mice than CR (Azami et al. 2018). Zarenezbad et al. study the leishmanicidal activity using nanoemulsion-based nanogel *Citrus limon* essential oil against *Leishmania tropica* and *Leishmania major*. This finding suggested that the toxic effect of *Citrus limon* was found to be more significant compared to *Mentha*

piperita, *Anethum graveolens*. Moreover, an 80 μg/mL concentration of CLN gel responsible for the complete inhibition of both species of leishmania in in vivo mice model (Zarenezhad et al. 2021).

9.3.4 Polymeric Nanoparticles

Polymeric NPs are solid colloidal suspensions consisting of natural and synthetic polymers used for nanosized drug delivery system. NPs allows therapeutic agents could be encapsulated, entrapped, dissolved and conjugated to their surface. For the drug delivery, polymeric NPs can be employed in variety of forms such as in NPs, nanospheres, or nano-capsules based on preparation methods and their physiochemical properties. In the golden age of pharmaceutical nanocarriers, polymeric NPs have been considered for sustained drug release, and targeted delivery to specific organs and tissues and due to such versatile nature, it offers multiple cargo (proteins, peptides and genes) delivery.

Currently, Elmi et al. synthesized biogenic Chitosan nanoparticles from *Penicillium* fungi to target human protozoal parasites—*Giardia lamblia*, *Plasmodium falciparum* and *Trichomonas vaginalis*. This study demonstrated that nano-chitosan exhibited excellent anti-parasitic activity by inhibiting the growth rate of cultivated *P. falciparum, T. vaginalis* and *G. lamblia* by 59.5%, 99.4%, and 31.3%, respectively with negligible toxic effects. This finding concluded that green synthesized Chitosan nanoparticles combat parasitic infection based on dose-dependent (Elmi et al. 2021). Although, polymer-based nanoparticles are extensively used to carry the drugs for intracellular parasites, for example, amphotericin B for *Leishmania* as reported in Asthana et al. (2015), and chloroquine and artemisinin for intracellular targeting of Plasmodium (Tripathy et al. 2013). In addition, layered assembly of gelatin nanoparticle encapsulated phthalocianato [bis(dimethylaminoethanoxy)] silicon (NzPC) and modified with polyelectrolytes (polystyrene sulfonate/polyallylamine hydrochloride) [PGN-NzPc] for PDT (photodynamic therapy) implementation in combating promastigote form of *Leishmania amazonensis*. The PGN-NzPc facilitated the lower toxicity in the dark while in the presence of PDT trigged the 80% killing of *Leishmania* promastigotes by altering the morphology (de Souza et al. 2021). Further Lima et al. prepared lignan (−)-6,6′-dinitrohinokinin (DNHK) loaded into poly(lactic-*co*-glycolic acid) nanoparticles (DNHK-loaded PLGA) against *Schistosoma mansoni*. This study concluded that DNHK-loaded PLGA NPs augmented the sustained release of DNHK to the infection site and showed remarkable potency in killing 100% population of adult worms. This DNHK-PLGA NPs have enhanced anti-schistosomicidal activity (Lima et al. 2017).

9.4 Future Perspective and Conclusion

Despite the quick expansion of parasitic diseases worldwide, exciting therapeutic approaches are essential to manage these diseases. But the existing conventional drugs for treating parasitic diseases are outdated, weak, ineffective with deadly toxicities, adverse effects and inducing elevated resistance to disease-causing pathogens. Various reports of re-purposing of conventional drugs via nano-formulations have shown significant responses by reducing their toxicity and enhancing the therapeutic efficacy coupled with low cost. Since, reports suggest that nanoformulations will increase efficacy by higher targeting efficiency, site-specific delivery, and enhanced bio-availability of the drug at the disease site. Therefore, more emphasis is to be given to systematic investigation and research related to the selection designing and fabrication of nanocarriers. Here, the physiochemical characteristics of nanoparticles can be a conclusive factor playing a decisive role in determining the effectiveness of nanocarriers in delivering antiparasitic drugs at a desired locus with a hope for improved pharmacokinetic and pharmacodynamic properties. Moreover, the research method with powerful technologies together can advance the treatment approach with more precision in in vivo research and clinical studies. Currently, no nano-formulations of anti-parasitic drug is available in the marketplace, lots of them are still in the process of better clinical trials, formulation designs, preclinical studies, and commercialization under the name of "antiparasitic nanomedicines". With constant efforts, efficient therapy will progress as an inevitable trend in pharmaceutical industries with antiparasitic nanomedicine shaving an infinite future against parasitic diseases controlling their spread.

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