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NANOTECHNOLOGY-DRIVEN STRATEGIES FOR TARGETED DELIVERY OF ANTIPARASITIC DRUGS: A REVIEW

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Abstract
Parasitic infections continue to pose a significant global health burden, particularly in tropical and subtropical regions. Traditional antiparasitic drugs often suffer from issues such as poor bioavailability, drug resistance, and non-specific toxicity. Nanotechnology has emerged as a promising approach for enhancing drug delivery by improving drug stability, targeting infected tissues, and reducing side effects. To treat protozoan and helminthic illnesses, this study examines recent developments in drug delivery systems based on nanotechnology, including nanoparticles, liposomes, dendrimers, and polymeric carriers. Additionally, we discuss the challenges, safety concerns, and prospects of nanomedicine in the field of parasitology.

INTRODUCTION

1.1 Parasitic infections

A class of pathogens known as parasites is more dangerous to people and animals than bacteria, and they typically cause chronic illnesses. Many parasite infections are rarely identified promptly, in contrast to the majority of bacterial infectious diseases, which have quick onset and clear symptoms and significant financial losses in animal husbandry (Roberts et al., 1994). Of the approximately 1500 agents that are known to be contagious to humans, 287 are helminths, and 66 are protozoa (Chomel, 2008;

Taylor et al., 2001). Parasitic diseases constitute a diverse collection of protozoa, helminths, or ectoparasites. It can be caused by several diseases which were recently estimated as the global burden of the most important neglected tropical diseases due to helminths and protozoa that the more than 5400 million people may be at risk, and more than 1.200 million might be infected (Utzinger et al., 2012). Filariasis, intestinal helminths, cysticercosis, and schistosomiasis are the most common helminth illnesses among immigrants. (Monge-Maillo et al., 2009; Norman et al., 2010).

One of the most common illnesses affecting both humans and animals is helminth infection (de Moraes & Geary, 2020). Parasitic helminth infections constitute some of the most prevalent human and animal infections. Toxocariasis, one of the most economically important and widespread zoonotic parasitic infections shared by humans and dogs, and cats, is caused by nematodes of the genus Toxocara (Mengarda et al., 2023). Human toxocariasis has few and ineffective treatment options, which often include corticosteroids to control inflammation and anthelmintic drugs (Dantas-Torres, 2020). The main medications are old and were initially created for veterinary use, just like the majority of antihelmintic medications used in people. There is currently no approved anthelmintic treatment for human toxocariasis. Only four drugs can be used for human treatment: albendazole, mebendazole, diethylcarbamazine, and thiabendazole. Toxocara's complex biology and lack of understanding of host tissue interaction pose significant challenges in treating toxocariasis. Current anthelmintics are outdated and often ineffective, and the lack of validated molecular targets hinders effective treatment (Mengarda et al., 2023).

Protists, or unicellular eukaryotes, are parasitic protozoans. They are also similar in that they are heterotrophic, motile in at least one stage, and rely on a host to survive. These organisms have the potential to cause serious illness and death in domestic animals, which could lead to considerable financial losses in the livestock industry or serious worries for pet owners (Schnittger & Florin-Christensen, 2018). Parasitic parasites are the vectors of some of the deadliest and most prevalent infections on the planet. Some of these members of the group of pathogens include the protozoans Trypanosoma (African sleeping sickness and Chagas disease), Leishmania (leishmaniasis), and Plasmodium (malaria), and the helminths such as Schistosoma (schistosomiasis), Wuchereria (filariasis), and Echinococcus (echinococcosis), among others. A majority of these infections have been long noted as tropical or subtropical **(Fearon et al., 2013).**

Ectoparasites of insects and arachnids exhibit a variety of associations with their hosts, ranging from obligatory to facultative, permanent to sporadic, and superficial to beneath the skin. Because ectoparasites can produce a variety of harmful effects, their activity infesting livestock and companion animals is particularly interesting (Van den Broek et al., 2003). Additionally, several ectoparasites serve as vectors for bacteria, viruses, cestodes, nematodes, and protozoa. The way ectoparasites behave also may result in indirect injury by upsetting the animal, increasing rubbing behavior, decreasing grazing or ruminating time, and even causing self-wounding (Berriatua et al., 1999).

1.2 Challenges in current antiparasitic drug treatments

The low bioavailability of antiparasitic drugs presents a significant challenge in effectively treating infectious diseases, particularly those prevalent in tropical and underdeveloped regions. Bioavailability refers to the proportion of a drug that enters the systemic circulation unchanged, a crucial factor for achieving therapeutic efficacy. Many available antiparasitic therapies suffer from low bioavailability, which often necessitates higher dosages, exacerbating potential toxicity and leading to poor patient adherence to treatment regimens. Current formulations fail to deliver adequate drug concentrations to target tissues, hindering their effectiveness against parasites, such as those causing Leishmaniasis and Chagas disease, where drug resistance is rampant (Souto et al., 2019). Recent advancements in drug delivery systems, such as biodegradable polyanhydride nanoparticles, show promise in enhancing the pharmacokinetic profiles of conventional antiparasitic therapies by ensuring sustained and targeted release, ultimately reducing dosage requirements and mitigating resistance

(Binnebose, 2018). These innovations highlight the urgent need for improved therapeutic strategies to combat low bioavailability in antiparasitic drug treatments.

1.3 Drug Resistance in Parasitic Infection

The emergence of drug resistance in parasitic infections poses a significant challenge to global health, severely complicating treatment protocols. As various protozoa, such as those responsible for Leishmaniasis and Chagas disease, exhibit increasing resistance to existing pharmaceutical treatments, the effective management of these diseases is jeopardized. Current antiparasitic drugs often yield limited therapeutic outcomes, as evidenced by the growing incidence of treatment-resistant strains of these microorganisms. Innovative approaches are essential in countering this issue, with recent advancements in drug delivery systems highlighting the potential for enhanced bioavailability and efficacy of conventional therapies. Furthermore, investments in nanobiotechnology show promise for treating neglected diseases by minimizing toxicity while improving drug accessibility and effectiveness (Souto et al., 2019). Such breakthroughs underline the critical need for sustained investment and research in this field, aimed at overcoming the barriers posed by drug resistance in parasitic infections (Islan et al., 2017). Resistance can arise through various pathways, including genetic mutations that enable parasites to detoxify medications or alter drug targets, ultimately undermining therapeutic efficacy. These adaptations underscore the urgency for developing new pharmacological agents that can circumvent existing resistance mechanisms. Recent advances in nanobiotechnology are promising as they enhance drug delivery and bioavailability while minimizing toxicity. By utilizing nanocarriers, researchers can improve the precision of drug action, potentially overcoming the challenges associated with current antiparasitic treatments (Islan et al., 2017).

1. Nanotechnology

One of the scientific frontiers today is nanotechnology. By enabling cyclic dosing, adjustable release of hydrophilic as well as hydrophobic drugs, and controlled release of therapeutic agents in a steady dosage for prolonged durations, existing polymeric research is essentially playing a role in developing nanotechnology (Bhatia & Bhatia, 2016).

Nanoscience has turned out to be a boon to humankind by providing a variety of benefits over traditional drug formulations. Later on, this triggered a re-strategizing of the game plan to fight diseases/disorders (Keservani et al., 2017). Over the past twenty years, an immense growth occurred in the sector of nanoscience. In his classic speech at the California Institute of Technology on December 29, 1959, Richard Feynman spoke publicly about the domain of nanotechnology for the very first time. In 1960, he presented his paper titled "*There Is Plenty of Room at the Bottom*"(Durán et al., 2005; Klaus et al., 1999).

Nanotechnology refers to the new branch of pharmacological sciences where the particles are of nanosize, and because of nano size, they become more reactive when placed side by side with their distinct counterparts (Gour & Jain, 2019). Nanotechnology, or nanoscience, refers to the study of materials at 100 nm or smaller, spanning numerous fields from material science to personal care. A principal area is nanomedicine, which includes medical interventions at the molecular level for disease prevention, diagnosis, and treatment (Park, 2007).

In 1970, the term nanotechnology was first defined by Norio Taniguchi. Nanoparticles are used in various fields, including chemistry, electrical engineering, and biological textiles. Depending on the size and shape of the metal particles, they have different applications (Crabtree et al., 2003; Matsumura et al., 2003; Wojtal et al., 2007).In recent years, Nanoparticles have been extensively studied because of their small size and increased surface-to-volume ratio, which result in their specific physical and chemical properties. Optical and catalytic properties (Zharov et al., 2005).

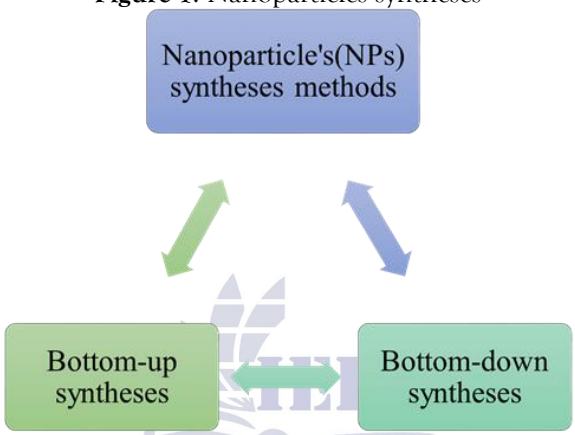
There are two categories of nanoparticles: inorganic and organic nanoparticles (Xu et al., 2006). Inorganic nanoparticles include semiconductor, magnetic, and noble metal nanoparticles, whereas organic nanoparticles comprise carbon nanoparticles (Drake & Hazelwood; Shaalan et al., 2007; Stav et al., 2005). The use of inorganic nanoparticles has increased because they are versatile in function,

providing medicinal imaging tools and high material properties (Cheon & Underwood, 2009). Semiconductor and metallic nanoparticles have intrinsic optical properties, which enhance polymer-particle transparency (Caseri, 2008).

2.1 Synthesis of nanoparticles

Nanoparticles can be synthesized through the Top-down method that comprises breaking larger solid particles into smaller ones (Iravani, 2011)and the Bottom-up method that collects and assembles gas or liquid molecules into defined structures(Makarov et al., 2014). The top-down approach is not reliable, as perfect surface nanoparticles cannot be obtained due to roughness. While in the bottom-up approach, seamless nanoparticles are obtained. Another advantage of this approach is that no waste materials are formed during this process, as small-sized nanoparticles are obtained (Iravani, 2011; Makarov et al., 2014). Nanoparticles are made from different techniques, e.g., physical and chemical methods. These methods require high consumption of energy, have low yield, are expensive, and cause damage to the environment (Cicek et al., 2015; Nadaroglu et al., 2017).

Figure 1: Nanoparticles syntheses



2.2 Nanotechnology Potential in Drug Delivery

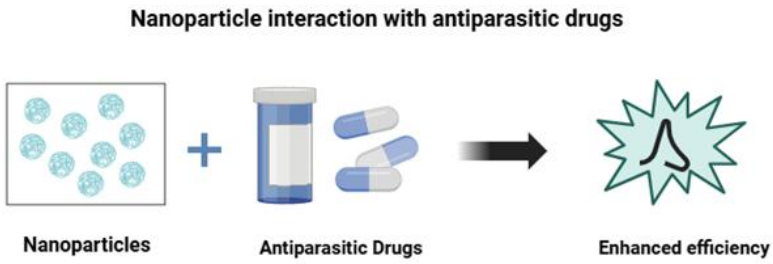
In the field of medication delivery, nanoparticles have become a revolutionary force, offering creative ways to get around the drawbacks of traditional drug compositions (Bennet & Kim, 2014). Nanosystems of drug delivery are a large part of nanomedicine. In drug delivery, it is useless to define nanotechnology based on a size cutoff since the utility and efficacy of drug delivery systems do not rest on their sizes alone. Practical drug delivery systems can span from actually being nanosystems (such as drug-polymer conjugates and polymer micelles) to 100-μm microparticles. Both nano- and micro-scale systems have been crucially vital in fabricating different clinically relevant drug delivery systems. For practical purposes, in this view, "nanotechnology" encompasses "microtechnology" and "nanofabrication" or "nanomanufacturing" and its micro counterparts (Park, 2007).

There is research being carried out all around the world on the advantages and disadvantages of nanotechnology and the applications of it in a very wide range of fields from material science and medicine to space studies. Nanotechnology is being implemented in medicine with nanoparticle-delivery drugs, nanoscale diagnostic tools, tissue engineering, and biosensors (Subramani et al., 2019).

These structures, usually between 1 and 1000 nanometers in size, have special physicochemical characteristics that can be used to improve medication solubility, improve bioavailability, achieve targeted delivery, and reduce adverse side effects. Nanoparticles can increase the bioavailability of drugs, shorten the decrease in release time, stop drug aggregation, shorten medication absorption time, and enhance the solubility of drugs in the bloodstream (Afzal et al., 2022). Nanoparticles' capacity to go beyond biological obstacles and interact with cells at the molecular level has opened up new avenues for treating several illnesses, including infectious infections, cardiovascular conditions, and cancer (Navya et al., 2019; Simonazzi et al., 2018). Nanoparticles are versatile platforms that can be customized with various functionalities

to achieve specific therapeutic goals (Alshamrani, 2022). Despite their great promise, developing nanoparticle-based drug formulations presents substantial obstacles that impede their successful clinical translation (Jayasinghe et al., 2022). These challenges encompass safety concerns, the intricacies of large-scale production, the necessity for well-defined regulatory frameworks, and issues about intellectual property (Dhapte & Pokharkar, 2019; Suman et al., 2023).

Figure 2: Nanoparticle interaction with antiparasitic drugs



2.3 Drug Delivery Systems

Nanoparticles have great potential as a successful drug delivery system. Nanotechnology is used for many developments in the form of drug delivery (Suri et al., 2007). Nanoparticles can be used in disease-targeted drug delivery at the disease site to assist in enhancing poorly soluble drug uptake, site-specific drug targeting, and drug bioavailability (Kipp, 2004; Ould-Ouali et al., 2005). At this point, many different nanosystems with different biological properties and compositions have been widely researched for application in drug and gene delivery. Cell surface receptor targeting, drug release, administration of multiple drugs, therapeutic agent stability, and the molecular mechanism of cell signaling responsible for the pathobiology of a given disease are all required for efficient drug delivery. Nanomaterials have also found successful application in the development of several anti-cancer drugs, such as doxorubicin, 5-fluorouracil, dexamethasone, and paclitaxel (Suri et al., 2007).

Drug delivery methods based on nanotechnology are being investigated to enhance the management of parasite illnesses (Baruah et al., 2017; Sun et al., 2019; Volpedo et al., 2019). Traditional therapies frequently have drawbacks like toxicity and the emergence of drug resistance (Baruah et al., 2017; Folliero et al., 2021). Nanotechnology offers the potential to overcome these challenges through site-specific drug delivery, improved drug effectiveness, as decreased toxicity (Ali et al., 2013; Baruah et al., 2017).Polymeric nanoparticles are nanoparticles made from polymers (Prokop et al., 2001). They can be designed for controlled drug release and offer a flexible drug delivery system for various medical applications (Hoyos-Ceballos et al., 2020; Prokop et al., 2001). For example, poly (lactic-co-glycolic acid) nanoparticles are used to encapsulate drugs (Ali et al., 2014). Metal nanoparticles like silver nanoparticles have gained attention for their potential to lessen adverse effects (Naz et al., 2017). Solid lipid nanoparticles and nanostructured lipid carriers are examples of lipid-based nanoparticles (Date et al., 2007). They possess a controlled and continuous release capability and are compatible with tissues and cells (Ahmadpour et al., 2019). Three-dimensional polymeric structures known as dendrimers are distinguished by their distinct structure, excellent water solubility, biocompatibility, and remarkable capacity to encapsulate a variety of compounds (Folliero et al., 2021).

Figure 3: Types of nanoparticles

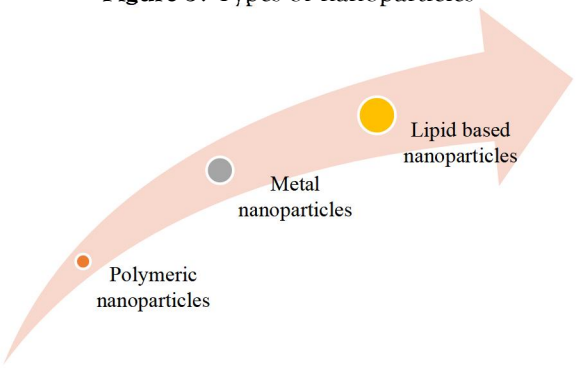


Table 1: Nanotechnology-based drug delivery systems

Parasite	Nanotechnology approach	Drug/Compound Used	Mode of Action	Reference
Leishmania spp	Silver nanoparticles (AgNPs)	Silver Nanoparticles	Generates reactive oxygen species (ROS) and disrupts cell membrane integrity.	(Allahverdiyev, Abamor, Bagirova, Ustundag, et al., 2011)
Plasmodium falciparum	Liposomal drug delivery system	Chloroquine-loaded liposomes	Enhances drug solubility and targeted release in infected cells.	(Hazarika et al., 2023)
Trypanosoma cruzi	Polymeric nanocarriers	Benznidazole-loaded nanoparticles	Increases bioavailability and reduces toxicity.	(Sousa et al., 2024)
Schistosoma mansoni	Chitosan-based nanoparticles	Praziquantel nanoformulation	Enhances drug absorption and prolongs circulation time.	(de Lima Nunes et al., 2021)
Toxoplasma gondii	Solid lipid nanoparticles (SLNs)	Spiramycin SLNs	Improves oral bioavailability and reduces systemic side effects.	(Karimi Yazdi et al., 2020)
Echinococcus granulosus	Metal-organic framework nanoparticles (MOFs)	Albendazole-loaded MOFs	Enhances drug retention and targeted intracellular delivery.	(Bajaj et al., 2022)
Cryptosporidium parvum	Nanoparticle-based oral drug	Nitazoxanide nanoformulation	Improves intestinal uptake	(AlFaleh et al., 2023)

	delivery system		and therapeutic effectiveness.	
Trichinella spiralis	Chitosan-based nano-drug carrier	Mebendazole-loaded chitosan NPs	Enhances solubility and bioavailability for systemic action.	(Henaish et al., 2025)

3. Targeting Mechanisms for Antiparasitic Nano drugs

Nanoparticles offer several targeting mechanisms to improve the delivery of antiparasitic drugs (Sun et al., 2019). These strategies aim to enhance drug efficacy, reduce toxicity, and overcome limitations of conventional treatments (Ali et al., 2013; Baruah et al., 2017). Specific drug targeting and delivery, increased safety and biocompatibility, quicker creation of new medications with broad safety margins, and enhanced pharmacokinetic behavior are the main goals in the development of Nano drugs (Onoue et al., 2014).

3.1 Passive Targeting

This approach relies on the inherent properties of nanoparticles to accumulate in the target site. The lymphatic endothelium and tiny capillary blood capillaries are easily penetrated by Nano drugs, potentially leading to longer circulation times and higher accumulation at target sites (Onoue et al., 2014).

3.2 Active Targeting

This entails adding certain ligands, like peptides or antibodies, to the surface of nanoparticles so they can attach to receptors or antigens on the surface of parasites or infected cells (Lin et al., 2015).

3.2 Stimuli-Responsive Nanocarriers

In reaction to particular triggers present in the parasite's surroundings or inside infected cells, these nanocarriers are made to release their pharmacological payload. Drug delivery systems based on nanotechnology have enormous potential to enhance the management of parasite infections by employing these targeted mechanisms (Ali et al., 2013).

3.3 Malaria

Malaria continues to be a major global health concern, with significant morbidity and mortality (Gujjari et al., 2022). The emergence of drug-resistant parasites and the limitations of current treatments highlight the need for new therapeutic approaches (Baruah et al., 2017; Gujjari et al., 2022). Drug delivery methods based on nanotechnology are being developed to minimize drug resistance, decrease toxicity, and enable site-specific drug administration (Baruah et al., 2017). Preclinical studies of antimalarial Nano formulations have yielded promising results (Chaves et al., 2022). While several preclinical formulations show promise, only a few have progressed to clinical trials (Chaves et al., 2022).

3.4 Leishmaniasis

Leishmaniasis, a neglected tropical disease, faces challenges in chemotherapy and drug development (Khan et al., 2018) . Nano-drug delivery systems are being explored to improve the safety and efficacy of existing drugs (Jamshaid et al., 2021). Topical nano-DDS, including niosomes, liposomes, and transfersomes, are being investigated for cutaneous leishmaniasis (Jamshaid et al., 2021). Self-emulsifying drug-delivery systems are also being developed to improve the delivery of hydrophobic drugs like curcumin (Khan et al., 2018). Mannosylated nano-DDS have been found to enhance macrophage internalization of drugs while minimizing toxicity (Jamshaid et al., 2021).

Nanoparticulate drug delivery systems are being explored for leishmaniasis, Chagas disease, and African trypanosomiasis (Volpedo et al., 2019). Nanopharmaceuticals are being developed to target lymphatic filaroids or Wolbachia and systemic microfilaria (Ali et al., 2013). Liposomes and solid lipid nanoparticles show potential for treating lymphatic filariasis (Ali et al., 2013).

3.5 Recent Advances and Case Studies

Nanotechnology-based treatments offer the potential for improved efficacy through targeted drug delivery (Ali et al., 2013; Baruah et al., 2017). Nanoparticles can be designed to accumulate at the site of infection, increasing the local drug concentration and enhancing the therapeutic effect (Pund & Joshi,

2017). This is particularly important in cases where the parasite is located in a difficult-to-reach area or has developed resistance to conventional drugs (Pandian et al., 2021). Traditional antiparasitic drugs often have significant side effects due to their lack of specificity (Pandian et al., 2021). Nanotechnology can improve the safety profile of these drugs by controlling their release and targeting them specifically to the parasite or infected cells (Jamshaid et al., 2021). This reduces the exposure of healthy tissues to the drug, minimizing adverse effects (Jamshaid et al., 2021). Nanoparticles can overcome biological barriers and deliver drugs to intracellular parasites, which are often inaccessible to traditional treatments (Pund & Joshi, 2017). Drug distribution to the target areas is made possible by the nanosize, which also improves cellular uptake, tissue tolerance, and effective transport across biological membranes (Pund & Joshi, 2017).

4. Limitations of nanotechnology in antiparasitic therapy

Nanoparticle-based treatments offer potential benefits like bypassing biological barriers and targeting disease sites. However, few have received clinical approval due to challenges in design, engineering, and manufacturing. Nanoparticles' intricate nature requires careful consideration of bio distribution, targeting sites, and potential immunological toxicities. Regulatory standards are not yet established for nanoparticle-based medicines, but efforts are being made to address these concerns (Desai, 2012).

5. Future directions

The future of antiparasitic therapy is poised to advance significantly through the integration of nanotechnology, particularly in the realms of personalized nanomedicine, combination therapies, and smart nanocarriers. Personalized nanomedicine involves tailoring treatment strategies to individual patient profiles, enhancing therapeutic efficacy, and minimizing adverse effects. Nanotechnology enables the design of customizable drug delivery systems that align with patient-specific treatment plans(Kumar et al., 2024). Combination therapies utilizing nanocarriers to co-deliver multiple therapeutic agents have shown promise in enhancing treatment efficacy and reducing the likelihood of resistance development. This approach enables synergistic effects by targeting parasites through various mechanisms (Allahverdiyev, Abamor, Bagirova, & Rafailovich, 2011). Additionally, the creation of stimuli-responsive smart nanocarrier systems that release their payload in response to particular biological cues can decrease off-target effects and increase targeting accuracy. These intelligent systems enhance the therapeutic index of antiparasitic agents (Kalombo et al., 2019). By addressing current challenges and embracing these future directions, nanotechnology can significantly advance the field of antiparasitic therapy, leading to more effective and personalized treatment options.

6. Conclusion

Nanotechnology offers a transformative approach to antiparasitic drug delivery by enhancing bioavailability, improving targeted therapy, and reducing side effects. Key findings highlight its potential to overcome drug resistance through combination therapies, enable personalized treatment strategies, and enhance precision with smart nanocarriers. However, challenges such as high production costs, scalability issues, regulatory hurdles, and biocompatibility concerns must be addressed. With continuous advancements, nanotechnology can revolutionize antiparasitic treatment, making it more effective and accessible. Nevertheless, further research and extensive clinical trials are essential to ensure safety, optimize formulations, and facilitate regulatory approvals for widespread application in healthcare.

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