



Nanotechnology in the Delivery of Protozoal Drugs: Enhancing Efficacy and Reducing Toxicity: A Review

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Abstract

Protozoan infections such as human African trypanosomiasis, leishmaniasis, Chagas disease, and malaria remain among the most pressing Neglected Tropical Diseases (NTDs), predominantly affecting developing regions. Conventional anti-protozoal therapies are limited by low efficacy, high toxicity, drug resistance, and poor accessibility. Nanotechnology has emerged as a transformative approach to overcome these challenges by enabling targeted, efficient, and safer drug delivery. Nanomaterials, owing to their unique physicochemical properties, including small size, large surface area, and modifiable surfaces, offer enhanced solubility, bioavailability, and pathogen-specific targeting while reducing systemic toxicity. Lipid-based nanocarriers, polymeric nanoparticles, and metallic nanostructures have demonstrated improved therapeutic performance against a range of protozoal pathogens. Amphotericin B-loaded solid lipid nanoparticles significantly reduced parasite burdens in visceral leishmaniasis, while pentamidine-SLN formulations improved efficacy against *Trypanosoma cruzi*. Polymeric nanoparticles encapsulating antigens or immunostimulatory agents have also shown promise in developing nanovaccines, providing robust immune responses and long-term protection in leishmaniasis and Chagas disease models. Moreover, nanoparticle systems have enhanced the solubility and targeted delivery of poorly soluble drugs against intestinal parasites like *Cryptosporidium parvum* and *Giardia lamblia*, and facilitated novel vaccine platforms against *Plasmodium falciparum* malaria using gold nanoparticles, virosomes, and virus-like particles (VLPs). Nanotechnology represents a powerful strategy for enhancing drug efficacy, minimising toxicity, and enabling innovative multi-drug and vaccine delivery systems. Continued interdisciplinary research and collaboration are essential to translate these advancements into effective, accessible therapies for protozoal diseases in endemic regions.

Keywords: Efficacy, Nanotechnology, Nanoparticles, Toxicity, Therapies

Introduction

Protozoan infections, including human African trypanosomiasis, leishmaniasis, Chagas disease, and malaria, are classified as Neglected Tropical Diseases (NTDs) that are endemic in developing countries and necessitate the urgent development of new drug therapies (Eltom et al., 2025). Current anti-parasitic treatments often have intrinsic limitations, such as low efficacy (or variable efficacy), high toxicity (or adverse effects), the appearance of resistant strains, and restricted availability or affordability (Saleem et al., 2025). Nanotechnology is emerging as a critical therapeutic avenue to overcome these longstanding challenges, providing novel delivery systems that enhance efficacy while minimizing adverse effects and reducing toxicity. (Abaidullah et al 2025). Delving into nanoparticle systems for enhanced drug delivery, nanotechnology is accelerating the evolution of drugs and vaccines because nanomaterials possess advantageous properties due to their size and surface area, allowing for encapsulation ability and serving as effective vehicles for antigen delivery and immunostimulatory agents (Abaidullah et al., 2025).
Nanotechnology: Enhancing Efficacy and Reducing Toxicity.

The field of drug delivery is rapidly innovating through advancements in formulation design and new technologies, such as nanotechnology (Akbari, 2025). Nanotechnology-based drug delivery systems offer a promising approach for fighting parasitic diseases (Deshmukh et al., 2025). Nanomaterials possess advantageous properties due to their size and surface area, including encapsulation ability, and can serve as effective vehicles for delivery (Choudhury et al., 2025). The use of nanomaterials allows for several key improvements over conventional drugs:

1. **Enhanced Targeting and Penetration:** Nanoparticles can improve the ability to specifically target pathogens and penetrate host barriers, allowing the drug to access areas where the pathogen resides (Bharti & Kumar, 2025). The optimal size of nanoparticles (NPs) decisively influences their biodistribution and interaction with immune system cells; particles smaller than 100 nm are efficiently taken up by targets such as dendritic cells (Jia et al., 2025). Controlling the physicochemical properties of nanoparticles, such as size, shape, surface charge, flexibility, hydrophobicity, and charge density, is key to optimizing a strong immune response and delivering nanoparticles to lymphatic vessels (Li et al., 2025). Strategies like surface functionalization with ligands, aptamers, or antibodies are critical for enhancing the precision and therapeutic efficacy of nanocarriers by achieving binding selectivity to disease-specific markers.
2. **Increased Solubility and Bioavailability:** Nanotechnology can increase the uptake of poorly soluble drugs. Encapsulating anti-infective agents within nanostructured carriers can enhance the stability and bioavailability of these compounds. For lipid-based drug delivery (LDD) systems, excipients like liposomes, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLCs) can improve the bioavailability of poorly absorbable and/or poorly soluble drugs (Pandey et al., 2025). Nanomaterials can also improve the circulation time of biological material and protect it from degradation, thus increasing its bioavailability (García et al., 2025).
3. **Toxicity Reduction:** Nanoparticles help reduce toxicity by minimizing the required dose amount and frequency of administration. The use of nanocarriers, such as LDD systems, leads to improved therapeutic efficacy with minimized side effects of the drug compounds. Advanced delivery systems, including surface functionalization and biopolymer encapsulation, can improve selectivity and effectiveness while reducing cytotoxicity (Kesharwani et al., 2025). For example, functionalizing Silver Nanoparticles (AgNPs) with biocompatible polymers or folic acid has been shown to enhance bacterial selectivity while reducing unintended cytotoxicity to human cells. Additionally, liposomal encapsulation shields nanoparticles (such as AgNPs) from premature degradation and reduces host toxicity by preventing direct interaction with mammalian cells. Developing advanced delivery systems for AgNPs, like pH-responsive or enzyme-triggered nanocarriers, can help achieve controlled and targeted release, enhancing antibacterial efficacy while minimizing exposure to healthy cells. Nanomaterials like polyanhydride NPs also possess favorable properties such as low toxicity and safety (Chaudhary et al., 2025).
4. **Multi-Drug Delivery:** Nanotechnology allows researchers to explore the possibility of multi-drug administration simultaneously by incorporating different anti-infective drugs into the same nanoparticle (Jin et al., 2025). These platforms can be designed based on the unique physicochemical properties of each therapeutic agent. This ability also allows for the design of multi-targeted systems, utilizing combinations of targeting cues (like pH sensitivity coupled with specific receptor-ligand interaction) to ensure delivery only to the intended site, improving selectivity and efficacy.

Nanoplatforms and Applications Against Protozoan Parasites

Several protozoal infections are being actively targeted using nano-based systems, demonstrating enhanced efficacy (Butt et al., 2025). Nanotechnology is accelerating the evolution of vaccines because nanomaterials, due to their encapsulation ability and advantageous properties derived from size and surface area, serve as effective vehicles for antigen delivery and immunostimulatory agents (Saleh et al., 2025).

Visceral Leishmaniasis and Chagas Disease (Trypanosomatid Infections)

Lipid-based nanocarriers, such as Solid Lipid Nanoparticles (SLN), have been studied to incorporate anti-infective drugs for different routes of administration and thus are useful for treating kinetoplastid protozoan infections.

- Amphotericin B incorporated into SLN produced a significant reduction of the parasite burden in experimental visceral leishmaniasis following oral administration. This highlights the utility of Amphotericin B-loaded nanoparticles as valuable chemotherapeutic approaches against leishmaniasis (Santos et al., 2025).

- Pentamidine incorporated into SLN was utilized for experimental infection with *Trypanosoma cruzi* (the causative agent of Chagas disease), also via oral administration (Heidari-Kharaji et al., 2025). Lipid-based nanocarriers have potential applications for Trypanosomatid-Caused Conditions.
- Nano-co-delivery systems using Poly(D, L-Lactide-Co-Glycolide) (PLGA) nanoparticles incorporating lipophosphoglycan and soluble/autoclaved *Leishmania* antigens have been evaluated for immunostimulatory effects against visceral leishmaniasis. Nano-optimization using biocompatible nanopolymers such as PLGA has achieved protection levels up to 80% against leishmaniasis (Jamshaid et al., 2025).
- An experimental nanovaccine offered total protection against successive infections and high control of parasite dissemination and replication against repeated exposures to *Trypanosoma cruzi* (Chowdhury et al., 2020), through the activation of a polyfunctional T cell response.

Cryptosporidiosis and Giardiasis

Nanoparticles prove valuable in combating intestinal protozoa, particularly by enhancing solubility and targeted delivery. Nanotechnology-based drug delivery systems are considered a promising approach for parasitic diseases, improving the ability to specifically target pathogens, penetrate host barriers, reduce toxicity by lowering dose amount and frequency of administration, and increase the uptake of poorly soluble drugs (Tiwari et al., 2023). A summary of the types of nanoparticles susceptible to parasites is shown in the sources.

Cryptosporidiosis (*C. parvum*)

Polymeric nanoparticles are among the systems used for treatment against *Cryptosporidium parvum* (Alfaleh et al., 2023).

- Chitosan nanoparticles were shown to reduce the number of *Cryptosporidium* oocysts.
- Polymeric nanoparticles incorporating Clofazimine successfully increased its solubility by 90 times, enhancing its potential as an anti-*Cryptosporidium* therapy. Clofazimine-loaded nanoparticles have also demonstrated long-term storage stability.
- Nano-suspensions containing Bupravaquone enhanced mucosal adsorption and targeting for treating *C. parvum*.
- Nano-Nitazoxanide (NTZ) incorporated into polymeric nanoparticles decreased the number of parasites, proving more effective at day 6 of treatment.
- Other polymeric nanoparticles, specifically those antibody-engineered with Indinavir, were able to target *C. parvum* in infected cells.
- Silver polymeric nanoparticles at high concentrations are able to fully break the oocyst wall of *C. parvum*. Copper oxide and silver polymeric nanoparticles also resulted in a significant reduction in cyst viability for *C. parvum* (Patravale et al., 2025).

Giardiasis (*G. lamblia*)

Nanoparticle approaches have shown significant promise against *Giardia lamblia* (syn. *G. intestinalis*).

- Encapsulation of a low dose of Metronidazole within Poly(D, L-Lactide-Co-Glycolide) (PLGA) nanoparticles improved the treatment compared to infected mice, leading to the complete elimination of cyst shedding and trophozoite count.
- A combination of silver, chitosan, and curcumin nanoparticles demonstrated the highest efficacy against *G. lamblia*, resulting in the elimination of the parasite from feces and the intestine.
- Gold nanoparticles exhibited effectiveness against *G. lamblia* cysts at a concentration of 0.3 mg/ml.

Malaria (*Plasmodium falciparum*)

Malaria, caused by the *Plasmodium* genus, is recognized as a notoriously fatal blood parasite, involving species such as *Plasmodium falciparum*, *P. vivax*, *P. ovale*, or *P. malariae* (Anwar, 2024). Developing a malaria vaccine remains challenging because of the complex life cycle of *Plasmodium* parasites (Etefia & Inyang-Etoh, 2023). Furthermore, parasite characteristics, such as the *P. falciparum* blood stage modifying the host red blood cell to acquire nutrients and evade destruction by the spleen, complicate treatment efforts (Belachew, 2018).

Vaccine development against protozoan diseases like malaria lags significantly behind that for viruses and bacteria. Despite efforts (including introductory pilot trials for the RTS, S vaccine, or Mosquirix, which offers partial protection in children), no widespread licensed vaccines have been achieved over the last 35 years. This complexity arises partly

because protozoan parasites have far more proteins than viruses, making it difficult to identify the right targets, and because they have evolved sophisticated immune-protective mechanisms (Celis-Giraldo et al., 2021). Nanovaccines are increasingly suggested as platforms for developing effective vaccines, building on the knowledge that CD8⁺ T-cell responses are essential for immunity against the parasite (Das & Ali, 2021).

Efforts involving nanomaterials date back 5–6 years:

- **Gold Nanoparticles (AuNPs):** Nanovaccines for malaria have been explored using the *Plasmodium falciparum* antigen Pf525 attached to gold nanoparticles (Kumar et al., 2015). Antigens designed to block transmission to mosquitoes have been tested on the surface of gold nanoparticles. These formulations successfully induced high titres of specific transmission-blocking antibodies (Abs) in mice, exhibiting functions similar to protective monoclonal antibodies (mAbs). This ability to induce Abs that compete with protective experimental mAbs places nanovaccine platforms in a highly advantageous position for future malaria vaccine development.
- **Virosomes and VLPs:** Virosomes have also been utilized against malarial parasites. For instance, influenza virosomes were adapted to deliver a non-adjuvanted, virosome-based PfCyRPA vaccine (a blood-stage *P. falciparum* cysteine-rich protective antigen). This delivery system induced strong growth-inhibitory Abs in preclinical in vivo and in vitro models, suggesting it can be further adapted as a multivalent and multi-stage virosomal anti-malarial vaccine (Westerfeld et al., 2006). Furthermore, novel Virus-Like Particle (VLP) vaccines encoding the Circumsporozoite Protein of *P. falciparum* were found to be immunogenic and elicit functional antibody responses in mice.

Conclusion

Nanotechnology offers powerful tools for developing more effective and safer anti-protozoal drugs, especially for neglected tropical diseases where current treatments are often hampered by high toxicity and variable efficacy. Nanoparticles, including solid lipid nanoparticles, polymeric nanoparticles, hydrogels, and dendrimers, facilitate targeted delivery, improve solubility, and reduce systemic toxicity, as demonstrated in applications against leishmaniasis (Amphotericin B in SLNs), Chagas disease (Pentamidine in SLNs), and intestinal protozoa (*C. parvum* and *G. lamblia* treatments). Continued investment and research collaboration between drug delivery scientists and pharmacologists specializing in anti-parasitic drugs are crucial to maximize the potential of these innovative delivery systems.

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