Nanoparticle-Based Drug Delivery System: A Review Of Recent Development And Challenges In Malaria

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Journal: International Journal of Nanobiotechnology

ISSN: 2456-0111

Review Article

Volume: 11

Issue: 1

Year: 2025

Article Received: 14th December 2024

Article accepted: 18th Febuary 2025

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Abstract

Malaria remains a global health challenge despite extensive efforts in prevention and treatment. Prompt diagnosis and effective treatment are critical for eradication efforts, yet resistance to current therapeutic drugs, particularly in Plasmodium falciparum and Plasmodium vivax, poses a major obstacle. Traditional antimalarial such as quinine, chloroquine, and artemisinin-based combination therapies have been widely used, but their effectiveness is increasingly compromised by resistance and pharmacokinetic limitations. Many antimalarial drugs suffer from poor bioavailability, off-target delivery, and suboptimal penetration into infected erythrocytes, leading to toxicity and reduced efficacy. Nanotechnology has emerged as a promising strategy to overcome these challenges by

enhancing drug stability, targeted delivery, and intracellular retention while minimizing adverse effects. Nanocarriers have been explored for encapsulating antimalarial agents, improving subcellular specificity, and protecting drugs from enzymatic degradation. This review examines recent advancements in nanotechnology-based drug delivery for malaria treatment and discusses the challenges associated with their application in this field.

Keywords- Nanoparticles, Malaria, nanotechnology, *Polymeric delivery systems, drug-delivery system*

Introduction

Globally, despite vast efforts in prevention and treatment, malaria continues to cause morbidity and mortality. Prompt diagnosis and effective treatment remain critical tactics for malarial treatment and eradication efforts. In humans, malaria is primarily caused by *Plasmodium* species including *P. vivax, P. falciparum, P. malariae, P. knowlesi* and *P. ovale*. Of these, *P. vivax* and *P. falciparum* are the most common and clinically significant species globally. Both species have overtime developed resistance towards the current therapeutic drugs, imposing a major obstacle in malaria elimination efforts [1].

Over the years, several treatments have been proposed and employed in treating malaria. Quinine, the first purified malaria treatment, shows efficacy against all *Plasmodium* species; schizonts [2, 3]. Although it is not the first line of treatment due to resistance, it is used in combination with clindamycin to treat uncomplicated malaria during pregnancy and for severe malaria [2, 4]. Other antimalarials drugs include mefloquine used for chemoprophylaxis and often combined with artesunate for uncomplicated malaria. Similarly, lumefantrine combined with artemether for treating uncomplicated *P. falciparum* malaria [2].

Chloroquine remains useful for treating *P. malarie*, *P. ovale,* and *P. vivax* malaria in areas without resistance whereas primaquine liver stages of *P. ovale* and *P. vivax.* Artemisinin derivatives including dihydroartemisinin arteether, artemether are commonly used in artemisinin-based combination therapies for uncomplicated malaria. The most common ACT drug combinations for treating uncomplicated malaria are dihydroartemsinin/piperaquine, artemether/lumefantrine and artesunate/sulfadoxine-pyrimethamine. On the other hand, proguanil/atovaquone is used for malaria prophylaxis and managing chloroquine-resistant strains [2, 5].

Apart from resistance, some antimalaria drugs have been reported to have poor bioavailability thus requiring high dosages resulting in adverse side effects [6]. Moreover, some are characterized by poor pharmacokinetic profile, off target delivery and inability to penetrate erythrocytes leading to accumulation of the drugs in non-targeted tissue and interaction with plasma proteins [7]. Focusing on the development of efficient drug delivery systems offers a promising strategy to surpass these drawbacks rather than emphasizing solely on discovering new drugs whose effectiveness is rapidly diminished by the parasite's resistance evolution. Moreover, the process of developing new drugs is a rigorous, time consuming and costly [5].

Within the array of strategies of malaria eradication, nanotechnology has emerged as a pivotal approach in developing effective drugs owing to their unique chemical, biological and physical properties that can be harnessed to address challenges in the management of malaria. Nanomaterials have been investigated for their capacity to encapsulate existing and emerging antimalarial agents and efficiently deliver them to specific targets sites. Therefore, they have a critical role in enhancing subcellular target specificity, intracellular retention and protect the drug from intracellular enzymatic degradation thereby improving efficacy and safety of antimalaria drugs [8]. The present review intends to analyse the recent development of nanocarriers that have been studied for malaria treatment. The review also covers the challenges of these nanocarriers in this field.

Development of nanomaterials against malaria

Nanotechnology in malaria diagnosis

Nanotechnology has recently been applied to improve the diagnostic tools already in place. Apart from clinical diagnosis, malaria diagnostic tools are based on specific *Plasmodium* biomarkers including unique parasite proteins such as lactate dehydrogenase, aldolase, histidine-rich protein II, and hemozoin a pigment marker. Detection of these markers involve direct microscope measurement of the parasite in blood sample, nucleic acid detection or antigen detection [9]. In addition, novel sensors which have been placed as simple, cost effective and rapid have been developed against *Plasmodium* biomarkers.

Previous studies have reported that nanotechnology- based diagnostic platforms can boost up detection of malaria at lower parasite level, offering a rapid, accurate, and sensitive method, which the tradition diagnostic tools are devoid of [8, 10]. Castro-Sesquen et al. [9] employed magnetic beads conjugated with anti-histidine-rich protein 2 (HRP2) antibody to detect and quantify *P. falciparum* HRP2 in serum and urine. Nanomaterials including magnetic and gold nanoparticles (AUNPs) coupled to the sensors has been shown to improve sensitivity and performance of the platform leading to better and precise diagnosis [101]. Moreover, molecular methods for diagnosis based on nucleic acids amplification tests (NAAT) have been improved through nanotechnology [11].

Nanotechnology in malaria treatment

At present, various drug combination has employed in the treatment of malaria including, ACTs. Despite showing therapeutic efficacy, there is still room to reduce their toxicity, prevent drug resistance, increase half-life and decrease the dosage for effective treatment [10]. In this regard, nanotechnology-based drug delivery system has been designed to target specific molecules, prevent drug from degradation, therefore, prolong blood circulation time, improve pharmacokinetic profiles, decrease dose frequency and thereby increase overall efficacy of treatments [12].

Polymeric delivery systems

Polymeric drug delivery systems have gained attention owing to their ability to control the release of drugs and adjust circulatory half-life properties. Hydrogels, polyplexes and micelles

are some of the responsive polymers for delivery of drugs with the ability to alter their physiochemical properties in response to external stimuli [13, 14]. With their unique hydrophilic shell structure that prolong drug's presence in the blood circulation, micelles are the most used polymers. Moreover, they can be functionalized with diverse ligands altering their permeability and hydrophobic core used to encapsulate and increase the solubility of poor water-soluble drugs [13, 15].

Polymeric particles including as chitosan, albumin and alginate have also been demonstrated to affect the kinetic of drugs thereby increasing biocompatibility. ~~Natesan et al. [16](16)~~ demonstrated that an artemisinin had a greater drug concentration when it was loaded with chitosan. The author attributed the increased bioavailability of the drug to the muco-adhensive properties of chitosan coat which interact with the mucus layer thereby increasing the residence at the site of absorption and assisting in attenuating drug release. Other polymeric delivery systems such as nanospheres, hydrogels and nanocapsules have been used to deliver antimalarial drugs. Whereas nanocapsules are vesicular systems characterized with hollow-core structures in which drugs are encapsulated within, nanospheres are solid core spherical particulates with a matrix in which the drug is embedded. To improve the efficacy, chloroquine loaded PLA nanospheres has been developed. The complex was prepared nanoprecipitation and emulsification solvent evaporation method. It was observed that the loaded PLA improved the uptake of chloroquine by the cell and elevated its activity [17].

Recent advancements in hydrogel-based drug delivery system have demonstrated significant promise in malaria treatment [18]. Composed of water-soluble polymers, hydrogels offer a biodegradable framework for safe and controlled drug delivery. For example, soy protein isolate-carbopol polyacrylamide-based hydrogels loaded with curcumin and chloroquine showed dual drug release with elevated rates at pH 7.4. Not only did this approach ensure slow of release of the drug but also permit the dual to address drug resistance. In addition, lumefantrine-loaded with hydrogels demonstrated improved release profiles while maintaining minimal toxicity and biocompatibility [19].

Vesicular drug delivery system

Liposomes

Liposomes, with their colloidal bilayer structure, encapsulate hydrophilic and hydrophobic drugs thereby protecting them from enzymatic degradation as well as elevate their efficacy. Sinha et al 2024). Co-loading lumefantrine and artemether into liposomes exhibited stability for 60 days at 4ºC, coupled with highly absorption in the liver and spleen, and a sustained drug release with minimal toxicity. Similarly, ~~Iravani & Varma~~ [20] reported that chloroquine-encapsulated liposomes administered in different routes in mice demonstrated higher drug concentration in the target sites compared to free chloroquine.

Niosomes, an alternative to liposomes have also been embraced in the management of malarial owing to their enhanced stability, cost effectiveness and versatility in drug delivery. Niosomes co-loaded with artemether demonstrated high drug entrapment efficiency and enhanced sustained release profiles. Additionally, curcumin and primaquine loaded with niosomes

showed superior antimalarial efficacy, enhanced drug bioavailability with minimal toxicity [21].

Recent advancement in ethosomal formulations for antimalarial drugs including febrifugine and artesunate have improved encapsulation efficiency, drug release and skin permeation compared to the conventional systems. Antimalarial drugs are encapsulated in ethosomes, flexible vesicles comprising of water, ethanol and phospholipids, designed to enhance transdermal drug delivery through their ability to increase skin permeability [22].

Solid lipid nanoparticles

Solid lipid nanoparticles have played a role in the development of effective antimalarial drug offering controlled release, enhanced drug stability and improved bioavailability. SLN are submicron colloidal carriers consisting of physiologically safe materials. They encapsulate antimalarial drug in a solid lipid matrix, protecting them from enzymatic degradation in the gastrointestinal tract. Studies have shown the potential of SLNs to enhance therapeutic efficacy as demonstrated by artemether-loaded SLNS which elevated permeability and dissolution with a biphasic release profile, and arteether-loaded SLNs, which depicted delayed metabolism and high entrapment efficiency [23].

Similarly, chloroquine-loaded with SLNs exhibited slow drug release and increased significantly the efficacy compared to free chloroquine [24]. Primaquine-loaded SLNs, prepared using a double-emulsification method and coupled with chitosan, exhibited prolong drug released and superior chemosuppression compared to free primaquine [25]. Moreover, dihydroartemisinin coupled with SLNs circumvent solubility challenges thereby achieving high release rate with enhanced *in vivo* efficacy [26]. Artesunate-loaded SLNs further demonstrated bioavailability, improved aqueous solubility and pH sensitive sustained release [23].

Carbon-based drug delivery

Recently, carbon-based nanoparticles particles such as graphene and graphene oxide, fullerenes, carbon nanotubes have drawn attention [8]. Due to their large surface area, permeability across the membranes, high drug-loading capacity, the carbon-based nanoparticles, are desirable choices for antimalarial drug delivery. Fullerenes derivatives such as C_{20}, C_{60}, C_{70}, are molecules composed of carbon atoms. Owing to their solubility in organic solvents, they readily accept electrons and aggregate readily in aqueous media. Nevertheless, addition of hydroxy groups to form fullerenols, can improve their solubility in water. Properties such as spherical shape, loading efficiency, antioxidant effects, capacity to sustain drug release and low adverse effects, make the derivatives ideal for drug delivery [27]. Regarding malarial treatment, in their study, ~~Novir and Aram~~ [28] demonstrated that the solubility and stability of chloroquine was enhanced when encapsulated with pristine C_{60} fullerene.

Previous studies have shown that carbon nanotubes can be employed to antimalarial drug carriers due to their desirable properties. A study by ~~Singh & Konwar~~ [29] demonstrated that artemether and its derivatives had high inhibitory effects against the translationally control tumor protein of *P. falciparum* using carbon nanotubes carriers.

Target specific nanoparticles

Active cell targeting has been considered effective in therapy of malaria diseases. Unlike passive targeting which employs common nanocarriers, active targeting involves the use of nanocarrier modified with ligands such as peptide protein, antibodies or carbohydrates. Liposomal formulation including those incorporated into maleimidophenyl butyramide phosphoethanolamine (MPB-PE) have exhibited antiparasitic effects by targeting and thereby inhibiting *Plasmodium falciparum*. Similarly, heparin-functionalized liposomes have increased the efficacy of encapsulated primaquine three times through synergistic parasiticidal while sparing healthy red blood cells. Nevertheless, complete parasite elimination poses a challenge [30, 31].

Metallic nanoparticles

Metallic nanoparticles including gold (AuNPs) and silver (AgNPs) are extensively being explored for antimalarial studies. Functionalization of AUNPs enhances their utility permitting for conjugation with drugs to target specific sites [32]. For instance, functionalizing Au(I) and (II) with ligands have exhibited efficacy against chloroquine-sensitive and chloroquine-resistant *P. falciparum* strains [33]. ~~Rai et al~~ [34] also reported that silver-based nanoparticles have efficacy against *P. falciparum*. In addition, glucose-based gold nanoclusters have demonstrated high specificity for *P. falciparum* sparing uninfected erythrocytes thereby improving drug efficacy.

Moreover, beyond treatment, AuNPs are explored as vaccine carriers enhancing immunogencity of antigens and offering promising platforms for transmission-blocking malaria [35]. On the other hand, silver nanoparticles have showed effectiveness against *P. falciparum* and malaria vectors due to their antiparasitic properties characterized by their ability to release bioactive silver ions that disrupt cellular membranes, hindering metabolic activities and eventually inducing necrosis and apoptosis in parasites [8].

Vaccine

It is documented that nanotechnology is an innovative platforms for developing malaria vaccines though the improvement of antigen stability, facilitating controlled release kinetic and enhancing immunogenicity [36]. Several drug candidates including Mosquirix has undergone clinical studies. Mosquirix utilizes virus-like particles at the nanometric scale to target specific proteins in *P. falciparum*. In addition, co-loading vaccines with lipid nanocarriers are being investigated for their potential to enhance immune responses against malaria [37].

Challenges

Potential toxicity of the nanoparticles is a major concern to human and the environment. For example, metal nanoparticles can generate free radicals leading to oxidative stress, which causes damage to cellular components including DNA, protein and lipids. Moreover, due to high reactivity, accidental exposure, accumulation of off-target nanomaterials and extended circulation time, several adverse effects including neurotoxicty, nephrotoxicity and

immunogenic responses have been observed following exposure to metal-based nanoparticles [38, 39].

Production of nanoparticles for therapeutic use is often costly and to some extent requires complex synthesis techniques. Scaling up the production of nanocarriers for mass production remains a significant challenge especially for low resource setting where malaria is prevalent. Lack of standardized protocol for the approval of nanomedicine pose a challenge since each type of nanoparticle require to meet stringent regulatory requirements for quality, efficacy and safety. Additionally, designing nanoparticle with the correct physical features and functionalization to ensure appropriate drug delivery is highly challenging. For this, a precise formulation is needed to maintain stability and prevent aggregation of nanocarriers which could affect their therapeutic efficacy [40].

Currently majority of studies concentrate on testing nanocarriers against a single Plasmodium species obtained from a single source, rather than investigating different species from multiple origins including clinical isolates. In addition, long-term studies on the effect of nanocarriers in vivo is still limited. Arguably, long term accumulation of nanocarriers in the body could lead to organic toxicity or interfere with biological functions [410].

Conclusion

Despite the progress made in malaria treatment, the current diagnostic and therapeutic options have limitations. Moreover, although ACTs drugs have exhibited good efficacy, factors such as adverse effects, poor aqueous solubility, unpalatability have resulted in poor patient adherence and eventually parasite resistance. The drugs also undergo elevated first-pass metabolism lack specificity and have lower efficacy that what it could potentially be. Nevertheless, it is well documented that nanomaterials present novel opportunities to overcome such hurdles through enhanced drug delivery, precise targeting, and sensitive diagnostic tools. Nanotechnology also has the advantage in further advancement of vaccine treatment modalities. These innovations aim to improve malaria treatment and contribute to the efforts towards malaria elimination and eradication goals. Despite the exciting development in malaria treatment, nanotechnology is not devoid of challenges including toxicity.

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