Design and therapeutic efficacy of polymer based drug delivery systems for antimalarials

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Malaria is a chronic and life-threatening disease. The currently used antimalarials suffer from drug resistance which is hindering the management of malaria world wide. There are also other factors that contribute to drug resistance of antimalarials such as poor quality of the drug, reduced uptake of the drug into the parasite, incorrect and inconvenient dosage schedules which usually result in patients non-compliance. The application of polymer-based drug delivery systems have been reported by several researchers to overcome drug resistance, toxicity and control the release mechanism of antimalarials. Some developed polymer based delivery systems used for the delivery of antimalarials with improved therapeutic effects include micelles, dendrimers, hydrogels, polymer-drug conjugates, liposomes and cyclodextrins etc. This chapter will evaluate the therapeutic efficacy of the presently developed polymer-based delivery systems used for encapsulation of antimalarials.

Keywords: antimalarial; polymer-based drug delivery systems; polymer-drug conjugates; dendrimers

1. Introduction

Malaria is a complex, chronic and life-threatening disease that varies in manifestation and epidemiology in different parts of the world [1]. These variations are as a result of the different species of malaria parasites, their susceptibility to the available antimalarials, environmental conditions and the level of immunity of the exposed human populations [1]. Several control and prevention measures have been developed to manage and control malaria transmission. However, some of these measures have not been found to be effective because of their inappropriateness and cost [1]. About half of the world’s population are at risk of the disease and the group of people prone to malaria infection are children, pregnant women, people living with HIV/AIDS and low-immune travellers from malaria-free areas [2]. Malaria can be prevented and treated. In a recent WHO report, the number of malaria infection globally reduced from 262 million in 2000 to 214 million in 2015 signifying an 18% decline [3]. Most cases of malaria infections are found in the sub-Saharan Africa, South-East Asia and the Eastern Mediterranean. Despite the reduction in malaria incidence worldwide, there is still a pressing need to develop drug systems that can further reduce the incidence of malaria infection. The number of malaria deaths globally was reported to have reduced from an estimated 839 000 in 2000 to 438 000 in 2015 indicating a reduction of 48%. Most of the deaths in 2015 were reported in sub-Saharan Africa, South-East Asia and Eastern Mediterranean [3]. Malaria is caused by Plasmodium parasites. There are five parasite species that cause malaria in humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Most deaths are caused by *P. falciparum* and *P. vivax* [4].

Malaria poses serious complications such as respiratory distress which is common in children infected with the disease caused by *P. falciparum*. Malaria infection in people living with Human Immunodeficiency Virus (HIV) also increases mortality rate. Other complications associated with malaria infections are stillbirth, severe headache, low birth weight, renal failure, encephalopathy, infant mortality rate, enlarged liver, low blood sugar, shock and spontaneous bleeding [5-10]. Malaria is treated using antimalarials and the currently used antimalarials suffer from severe pharmacological limitations such as drug resistance and toxicity. The aforementioned factors result in malaria treatment failure. Other factors that contribute to treatment failure are poor drug quality, misdiagnosis, incorrect dosing, poor patient compliance with the duration of dosing regimen and drug interactions [1]. Due to the widespread drug resistance, common manifestation of drug toxicity and poor patient compliance to duration of dosing regimen of antimalarials, there is a pressing need to develop drug delivery systems that can overcome drug resistance, reduce toxicity and improve patient compliance. This chapter will focus on the different types of polymer based drug delivery systems developed for delivery of antimalarials and their therapeutic efficacy.

2. Malaria cycle

After an anopheles mosquito bite, sporozoites are injected into the bloodstream and they travel to the liver where they develop into merozoites. The merozoites are released into the bloodstream where they invade the red blood cell and reproduce asexually to form new merozoites. Some of the merozoite-infected blood cells develop into male and female gametocytes that circulate in the bloodstream. If the anopheles mosquito bite a person whose blood contains the gametocytes form of the malaria parasite, the gametocytes will be taken up by the mosquito. In the mosquito’s stomach, the gametocytes develop into gamete and fuse to form zygote. The zygote develop to form ookinete after fertilization.
Ookinete is transformed to oocyst which multiplies in the stomach-wall of the mosquito to form sporozoites. The sporozoites migrate to the salivary glands of the mosquito. If the mosquito bites another person at this stage, it injects saliva containing parasites into another human being, and the cycle will be repeated [11-13]. P. ovale and P. vivax persist in the liver of an infected patient and usually result in relapse which occurs by invading the bloodstream weeks or years after infection [14] (Fig. 1).

Fig. 1 Malaria cycle

2.1 Currently used antimalarials and their mode of action

Antimalarials are classified based on their actions on the different phases of the parasite life cycle. They are classified as prophylactic, gametocytocidal, sporontocidal and schizontocidal.

In the context of malaria control, the use of prophylactic antimalarials are of great benefits to non/low immune travelers from endemic countries, children and pregnant women [15]. They disrupt the development of malaria parasites in the liver by hindering asexual blood stages of the parasite or by preventing the relapse of P. vivax and P. ovale malaria induced by hypnozoites [15,16]. Some examples of prophylactic antimalarials are primaquine, proguanil and pyrimethamine [17]. Gametocytocidal drugs are effective against the sexual forms of parasites in the blood. They prevent the transmission of malaria infection to the mosquito. They are useful because they reduce the rate of transmission and spread of drug resistance [17,18]. Some examples of gametocytocidal drugs are chloroquine, primaquine and artemisinin [17]. Sporontocidal drugs prevent the transmission of malaria infection by hindering the development of oocysts in the stomach wall of the mosquito that has fed on gametocytes [18]. Examples of sporontocidal drugs are primaquine, pyrimethamine and proguanil [17]. Schizontocidal antimalarials act on the asexual erythrocytic forms of all species of malaria parasites and the target the parasite food vacuole [19]. Example of schizontocidal drugs are proguanil, pyrimethamine, quinoline-containing drugs and artemisinin-based compounds [19].

Antimalarials are also classified into three classes based on their chemical structure and mode of action namely: quinolines, antifolate and artemisinin compounds [20]. Quinolines are the oldest and first class of antimalarials that were used for the treatment of malaria. The mode of action of a known quinoline compound i.e. chloroquine is by interaction with heme detoxification. There are reports of drug resistance of quinolines which are believed to be due to selected factors such as poor quality of drug and fast efflux of the drug from the parasites hindering inhibition of haem polymerization [21,22]. Antimalarials classified as quinolines are chloroquine, amodiaquine, mefloquine, piperaquine etc. Primaquine, an 8-aminoquinoline is very useful in preventing human to human malaria transmission [23]. Primaquine is used in combination with a blood schizontocidal agent for enhanced therapeutic effects [23]. Quinolines are also further classified as aminoquinolines and aryl-amino alcohols.

Antifolates act on the folate metabolism of the parasite. They are classified as inhibitors of dihydrofolate reductase (DHFR) e.g. pyrimethamine, proguanil and inhibitors of dihydropteroate synthase (DHPS) e.g. sulfadoxine, dapsone etc. Both DHFR and DHPS inhibitors are used in combination for synergistic effects [24]. The combination have been reported to develop resistance [23]. Artemisinin compounds are blood schizontocides and are active against all Plasmodium species. They exhibit a broad activity against asexual parasites, killing all stages from young rings to schizonts. They have high efficacy, fast action with reduced development of resistance [23]. They block malaria transmission, however they do not prevent transmission of mature gametocytes that is present at the time of treatment [23] and their mode of action is not clear.

2.2 Drug resistance and mechanism of resistance

The emergence of resistance in Plasmodium specie is dependent on multiple factors such as the rate of mutation of the parasite, poor quality of drug, poor-patient compliance and drug selection [25]. The rate of mutation of the parasite influences the rate of emergence of resistance. The main reason why malaria is difficult to control is due to its genome's
ability to mutate away from drug pressure [26]. A higher mutation rate results in a faster emergence of resistance and accumulation of deleterious mutations [25].

Poor quality of drugs such as counterfeit antimalarials usually result in parasites being exposed to sub-optimal blood concentrations of the drug. Factors that contribute to counterfeit antimalarials are self-treatment through the private sector that are not regulated, cost of treatment, poor accessibility of good quality antimalarials and lack of drug regulations [27]. Poor quality of antimalarials is a contributing factor to drug resistance. Non-patient compliance contributes to drug resistance and is due to patient's poor understanding of the disease, treatment and the relationship between patients and nurses [28].

The mechanism of resistance of antimalarials is complex, differs and is influenced by multiple genes. In quinine the genes associated with altered quinine response are: [25] pfcrt (P. falciparum chloroquine resistance transporter), pfmdr1 (P. falciparum multidrug resistance transporter 1) and pfhe1 (P. falciparum sodium/proton exchanger 1) [25]. Chloroquine resistance in P. falciparum is attributed to mutations in a gene encoding a transporter (PfCRT) and PfCRT [29]. However role of PfMDR1 mutations in chloroquine treatment remains unclear [29]. In antifolates, resistance to DHFR and DHPS inhibitors is due to single mutation of the gene encoding for the respective enzyme which results in substitutions in the amino acid chain [30].

2.3 Combination therapy

Using two or more antimalarials with different mechanisms of action has the potential to inhibit the development of resistance of the parasites to the drugs [1]. Application of combination therapy for the treatment of malaria has been found to prevent drug resistance and improve drug efficacy. Peters et al., reported that combination of antimalarials delay selection of resistant mutants in vitro [31]. However, despite the application of combination therapy for the treatment of malaria infection, resistance is still a major factor hindering global management of the disease. The emergence of drug resistance from combination therapy is attributed to the drug mode of action which is susceptible to parasite mutations or because resistance had developed already to one of the drug and mismatched pharmacokinetic properties of the drugs [32]. Various combination therapies are used for treatment of malaria however, artemisinin-based combination therapies are preferred because they lower malaria incidence and decrease the rate of emergence of drug resistance [32]. Some of these combination therapies are recommended as first-line treatments for uncomplicated P. falciparum malaria in malaria endemic countries. The artemisinin-based combination therapies recommended by WHO are: artether-lumifantrine, artesunate-mefloquine, artesunate-amodiaquine, artesunate-sulfadoxine/pyrimethamine and dihydroartemisinin–piperquine [1,33]. Artemisinin derivative in the combination has a short half-life and kills the parasites faster while the partner drug has a longer half-life and clears the remaining parasites. However they suffer from pharmacological limitations such pharmacokinetic mismatch and resistance [34].

3. Polymer based drug delivery systems

Design and application of polymer based drug delivery systems offer several benefits such as improves the bioavailability of the drugs, biocompatibility, reduces drug toxicity, enhances drug solubility, mask drug taste, improves drug release kinetics, protects the drug from enzymatic degradation while in circulation, enhances patients’ compliance to dosing regimen and can overcome drug resistance [35]. Several polymer based drug delivery systems have been developed such as micelles, polymer-drug conjugates, nanoemulsions, liposomes, dendrimers, nanospheres, nanocapsules, hydrogels, cyclodextrin etc.

3.1 Liposomes

Liposomes are drug delivery systems that consist of an aqueous core surrounded by a lipid bilayer (Fig. 2). The lipid bilayer separates the inner aqueous core from the outer layer. They are composed of natural phospholipids and are classified according to their lamellarity (i.e. uni-, oligo-, and multi-lamellar vesicles), size (i.e. small, intermediate, or large) and preparation methods [36]. They modify drug absorption, reduce metabolism, prolong biological half-life and reduce toxicity [37]. They are biocompatible and biodegradable which make them suitable and very useful for drug delivery. There are several research reports on liposomes encapsulated with antimalarials.

![Fig. 2 Schematic diagram of a liposome.](image)
The drug release profile of drugs from liposomes is dependent on the degradation of polymeric materials and some of them exhibit insufficient initial release. There is a possibility of high release of drug during high rate of degradation resulting in toxicity and they are expensive to prepare [38].

Issachi et al., prepared liposomal delivery systems encapsulated with artemisinin, artemisinin and curcumin [39]. The formulations was useful for parenteral administration and in vivo antimalarial analysis was performed on Plasmodium berghei NK-65 infected mice. The liposomal formulation exhibited immediate antimalarial effect with modified drug release [38]. Marques et al., adsorbed heparin onto positively charged liposomes followed by loading of primaquine whereby, heparin acts as antimalarial and targeting moiety [40]. The formulation exhibited three fold antiplasmodial activity in Plasmodium falciparum cultures than the free drugs [40]. Chimamaka et al., developed liposome formulations containing beta-artemether. In vivo analysis on mice infected with virulent rodent malaria parasite Plasmodium chabaudi exhibited a 100% cure after administration of the formulation [41]. Urbán et al., developed immunoliposomal nanovector for the targeted delivery of its chloroquine exclusively to Plasmodium falciparum-infected red blood cells [42-44]. The formulations showed improved efficacy. Same formulations were prepared containing chloroquine and fosmidomycin. Immunoliposome encapsulated with chloroquine and fosmidomycin exhibited tenfold efficacy of the antimalarial drugs [42]. Slabbert et al., entrapped mefloquine in liposomes and Pheroid™ vesicles. Meltoquine loaded Pheroid™ vesicles were stable and were found to be potential drug delivery system for antimalarials [45]. Arica et al., prepared liposomal formulations of primaquine diphosphate. In vivo analysis was performed by intravenous administration on Swiss Albino mice [46]. The in vivo results suggested that the liposomal formulations are potential antimalarials. Hasan et al., studied the inhibition of Plasmodium falciparum by stearylamine based liposomes. The chain length of alkyl group and density of stearylamine in the liposomes were significant factors that inhibited the growth of the parasites [47]. Similar report was reported by Rajendran et al., in which monensin loaded onto PEGylated Stearylamine liposome exhibited therapeutic potential against malaria infections [48]. Gabriëls and Plaizier developed sterile liposomes suspension for parenteral administration. The suspension was very stable at acidic pH [49]. Bayomi et al., prepared liposomal formulation containing arteether, a potent antimalarial agent [50]. In vivo evaluation was studied orally and intravenously on New Zealand rabbits. The formulation enhanced the bioavailability of arteether with longer elimination half-life [50]. Owais et al., covalently attached fragments of a mouse monoclonal antibody (MAb) and MAb F10 isolated from the Plasmodium berghei-infected mouse erythrocytes to the surface of liposome followed by loading with low dose of chloroquine. In vivo work was performed on the mice infected with chloroquine-resistant P. berghei. The liposomes were delivered intravenously and a cure rate of 75 to 90% was reported [51]. There are other researcher reports on the application of liposomes for delivery of antimalarials with enhanced therapeutic effects in vivo [52,53].

3.2 Polymeric Micelles

Polymeric micelles consist of a hydrophobic core and hydrophilic polymeric chains (Fig. 3) exposed to the aqueous environment [54]. Their sizes ranges between 10 -100 nm. They are useful for encapsulation of drugs with poor water solubility, they are stable and increase drug bioavailability. The hydrophilic chain enhances its stability in a dispersed state, decreases drug interactions with the cells and proteins [54]. Due to their unique properties, they are used for delivery of bioactive agents including antimalarials. Bhadra et al., developed polymeric micellar system for controlled delivery of artemether. Their systems enhanced the solubility of artemether significantly and prolonged the release of artemether to between 1-2 days in vitro [55]. However, they exhibit low drug loading capacity [56].

![Diagram of polymeric micelles loaded with drug molecule.](image)

3.3 Cyclodextrins

Cyclodextrins are a class of macrocyclic oligosaccharides connected by α-1,4 glycosidic bonds. They exhibit low toxicity, low immunogenicity, increase drug solubility and stability, enhance drug absorption, mask odours, tastes and control drug release profiles [57].

Chadha et al., encapsulated artemether onto β-cyclodextrin derivatives [58]. In vivo studies on four to five weeks old BALB/c mice suggested that encapsulation of the drug onto cyclodextrins increased the antimalarial activity by 3 fold with 100% eradication of parasites and enhanced the bioavailability of the drug when compared to the free drug [58]. Wong and Yuen et al., incorporated artemisinin onto cyclodextrin derivatives (alpha and gamma) and observed an improved oral drug bioavailability [59]. Crandell et al., investigated the antimalarial activity of sulfonated cyclodextrin [60]. Hartell et al. reported the complexation of antimalarials with cyclodextrins resulting in enhanced drug solubility [61]. Kakran et al., fabricated with β-cyclodextrin hydrophilic carrier for delivery of artemisinin nanoparticles by evaporative precipitation of nanosuspension [62]. Charman et al., developed cyclodextrin-based formulation containing ozonide, an antimalarial [63]. In vivo analysis was performed by intravenous administration on rat. An 8.5-fold decrease in
the steady-state blood volume of distribution, a 6.6-fold decrease in the mean residence time and a greater than 200-fold increase in renal clearance was observed from the formulation when compared to the free drug [63,64]. Yaméogo et al., reported a one-step transesterification of cyclodextrins encapsulated with artemisinin. In vitro antimalarial activity showed that the formulation inhibited the growth of multi-resistant K1 and susceptible 3D7 strains cultured Plasmodium falciparum [65]. Usuda et al., reported enhanced solubility of artemisinin by incorporating it onto derivatives of cyclodextrin [66]. Mahjan et al., reported the encapsulation of artmether onto hydroxypropyl-[β]-cyclodextrin for nasal delivery. The formulation also enhanced the drug stability at accelerated conditions over the period of 90 days. It was found to be an effective delivery system for the nasal route and useful for cerebral malaria [67].

3.4 Polymer-drug conjugates

Incorporation of drugs onto polymers via selected linker results in the formation of polymer-drug conjugates. The conjugation of drugs onto hydrophilic polymers changes the properties of the drug. Polymer-drug conjugates offer several advantages such as [68]: (i) increased water solubility; (ii) enhanced bioavailability (iii) temporarily protection of conjugated drug from degrading enzymes; (iv) reduced immunogenicity, toxicity and antigenicity and (v) specific accumulation in organs, tissues or cells. A polymer-drug conjugate (Fig. 4) consist of polymer backbone, the incorporated drug, the spacer, the targeting moiety and the solubilising group [69]. However, the main challenges associated with polymer drug conjugates in combination therapy are identification of drug ratios and combination and poor drug loading capacity [70]. There is very little research reports on polymer drug conjugates containing antimalarials.

![Polymer-drug conjugates](Fig. 4)

Urban et al., developed polyamidoamines encapsulated with chloroquine and primaquine that inhibited in vitro growth of P. falciparum [71]. Rajic et al., incorporation primaquine onto polymers to form conjugates. The conjugates exhibited high drug loading capacity of 14.2% to 32.9% (w/w) [72]. Tripathy et al. conjugated chloroquine to chitosan–tripolyphosphate (CS–TPP) nanoparticles for drug delivery against rodent parasite. They were found to eliminate and protect the lymphocytes, serum and RBC against P. berghei infection [73]. Aderibigbe et al., reported the preparation of polymer-drug conjugates containing antimalaria drugs (4 and 8-aminoquinolines). Some of the conjugates were found to exhibit antimalaria activity against the chloroquine sensitive strain of P. falciparum [74-76]. Kumar et al., developed polymer drug conjugates containing primaquine and dihydroartemisinin using substituted polyphosphazenes as polymer [78]. In vivo antimalarial efficacy of the conjugates was tested on Plasmodium berghei (NK65 resistant strain) infected Swiss albino mice at different doses. The conjugates exhibited antimalaria efficacy at lower doses with no recrudescence [78].

3.5 Dendrimers

Dendrimers are three-dimensional, star shaped, branched, macromolecules (Fig. 5). They possess low polydispersity index, they exhibit high water solubility, biocompatibility, polyvalency and precise molecular weight [79]. These properties make them ideal carriers for drug delivery [79]. They are made of three parts namely: a central core, building blocks with several interior layers and the exterior layer. Most of them possess molecular diameter of less than 10 nm which are similar sizes and shapes of specific proteins thereby making them perfect biomimics [80]. Their exterior layer is made up of functionalities useful for bio-conjugation of drugs, signalling groups, targeting moieties or biocompatibility groups [80]. The interior layers have spaces suitable for encapsulation of drug molecules with enhanced drug efficacy: reduced drug toxicity and controlled release mechanisms. They are biocompatible and can be easily excreted from the body after drug release because of their nano-size.
Ndior et al., recently reported the synthesis of polypropyleneimine dendrimers containing 2-hydroxy-p-naphthoquinoline [81]. Bhadra et al., prepared similar polypropyleneimine dendrimers which were coated peripherally with galactose for delivery of primaquine phosphate to the liver cells. They were synthesized by Michael addition reaction of ethylenediamine followed by hydrogenation reaction. In vivo analysis was performed and results obtained suggested that coating of the dendrimers with galactose resulted in increased drug entrapment efficiency and sustained drug release for up to 5-6 days. Further studies such as: haemolytic toxicity, blood level and haematological studies confirmed the safety and suitability of these systems for sustained delivery of primaquine to the liver [82].

Agrawal et al., synthesized and performed in vivo analysis on coated and uncoated poly-L-lysine dendrimers having polyethyleneglycol (PEG-1000) loaded with chloroquine phosphate. The dendrimers exhibited controlled drug release profile. The coated drug dendrimer exhibited reduced haemolytic toxicity than the uncoated dendrimers and the free drug. These findings suggested that the coated dendrimers are less immunogenic than the uncoated formulations [83]. Movellan et al., reported polyester dendrimers based on 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) and Pluronic® polymers encapsulated with chloroquine and primaquine. They dendrimers exhibited specific targeting ability to pRBCs with reduced in vitro IC₅₀ for chloroquine and primaquine [84].

3.6 Nanocapsules

Nanocapsules are nano-vesicular systems (Fig. 6) consisting of an inner liquid core and an outer polymeric membrane [85]. The drug is loaded in the inner core surrounded by polymer membrane. The inner core contain the active substance which can be solid, liquid or dispersion [85]. Their applications offers several advantages such as targeted and sustained release, enhance drug bioavailability and reduces drug toxicity. They can be administered intravenously and they deliver drug directly to the target site with reduced dosage [86].

Haas et al., developed quinine-loaded nanocapsules. In vivo analysis was performed on Plasmodium berghei-infected Wistar rat so as to evaluate their efficacy in vivo and to determine their pharmacokinetics and erythrocyte partition coefficient using different dosing regimens. Intravenous administration of quinine loaded nanocapsules resulted in 100% survival which was a 30% reduction compared with the free quinine. Encapsulation of quinine onto the nanocapsules enhanced the interaction between quinine and the erythrocyte [87]. Mosqueira et al., developed nanocapsule of halofantrin from polylactide homopolymers [88]. The efficacy and pharmacokinetics of the formulation were studied in mice infected with Plasmodium berghei. The formulations were not toxic after intravenous administration. The drug loaded nanocapsules were found to control parasite development faster in the first 48 h post treatment. These results suggested that nanocapsule formulations of halofantrine reduced the intravenous dose and toxicity, thus is useful for parenteral route in severe malaria [88]. Leite et al., studied the reduction in halofantrine toxicity by loading it onto poly-ε-caprolactone nanocapsules [89]. The drug loaded nanocapsules exhibited greater efficacy in P. berghei-infected mice than the free drug. The treatment with the free drug resulted in bradycardia and severe hypotension leading to death whereas reduction in cardiac toxicity was observed in nanocapsules encapsulated with halofantrin [89]. Legrand et al., developed nanocapsules for delivery of halofantrin [90]. The nanocapsules loaded with halofantrin exhibited high percentage of encapsulation and were physically stable. The release of halofantrine was dependent on the partition between oil and external medium [90]. Alves et al., encapsulated porphyrin derivatives onto micro- and nanocapsules of marine atelocollagen. The IC₅₀ of some encapsulated metalloporphyrins showed an 80-fold
increase in antimalarial activity when compared to non-encapsulated porphyrin [91]. Deda et al., reported an overview of nanocapsules loaded with porphyrins as potential antimalarial formulations [92]. Anand developed nanocapsules composed of alginate-enclosed, chitosan-conjugated, calcium phosphate buffalo which were effective against rodent parasite Plasmodium berghei [93]. The nanocapsules reduced the parasite load in mice compared significantly by changing the expression of miRNAs and enhanced uptake in various organs resulting in inhibitory effect against the parasite as well as maintenance of the Fe metabolism [93].

3.7 Hydrogels

Hydrogels are three-dimensional (Fig. 7), cross-linked networks prepared from any water-soluble polymers [94]. They can be prepared in different forms such as films, slabs, microparticles, coating and nanoparticles [94]. They have porous structure that can be easily modified by the degree of the density of cross-links in their matrix and their affinity for the aqueous environment in which they are swollen. Their porous structure is useful for loading and release of drugs and is dependent on the diffusion coefficient of the drug molecule through the network [94]. Hydrogels exhibit several properties that are useful for biomedical applications such as: biocompatibility, environmental sensitivity (e.g. pH, temperature and electric field), control the rate of drug release, patient compliance and biodegradability [94].

Musabayane and Munjer developed amidated pectin matrix patch for transdermal delivery of chloroquine so as to overcome the bitter taste associated with oral administration [95]. The intravenous and transdermal administration of chloroquine were compared using Sprague-Dawley rats. The plasma chloroquine concentrations from the intravenous application hydrogel matrix patch were 9.3 ± 0.8 mg L$^{-1}$ and 7.3 ± 1.1 mg L$^{-1}$, respectively. The results suggested that the pectin chloroquine patch matrix preparation is a potential device for transdermal delivery of chloroquine [95]. Munjeri et al., developed amidated pectin beads loaded with chloroquine in which the ratio of pectin to chloroquine were varied [96]. In vitro release studies of chloroquine from pectin hydrogel beads in simulated gastric and intestinal fluids showed that the total release of chloroquine in gastric fluid was slow when compared to the simulated intestinal fluid. The total drug release from the simulated intestinal fluid was obtained over a period of 7 hours whereas the total drug release in simulated gastric fluid was not achieved. The plasma pharmacokinetics of chloroquine from pectin hydrogel beads and chloroquine diphosphate solution were compared using Sprague-Dawley rats over a period of 60 h. The hydrogel pectin beads were found to be potential drug delivery systems for sustained release of antimalarials resulting in longer dosing intervals, reduced cardiotoxic effects and impairment of kidney function [96]. Aderibigbe et al., developed gum acacia containing hydrogels for controlled dual-drug delivery of 4-Aminoquinoline analog and curcumin. 4-Aminoquinoline analog exhibited a short term release profile while curcumin exhibited a sustained and long term release profile. The preliminary results suggested that these systems are potential dual-drug delivery system for antimalarials with different pharmacokinetics [97]. Dreve et al., synthesized and characterized chitosan-based hydrogels for delivery of quinine. Quinine was found to form temporary chelates in the hydrogels [98]. Frigeri et al., prepared low molecular weight gels which were sensitive to light and pH [99]. Release kinetics of 8-aminoquinoline and 2-hydroxyquinoline from the gels were studied. The release of 2-hydroxyquinoline from the gels was found to be faster than that of 8-aminoquinoline. The initial release of 8-aminoquinoline was by gel degradation suggesting that 8-aminoquinoline has a strong interaction with the gelator molecules. These results further indicated the potential of the gels as delivery vehicles for small drug molecules [99]. Nishi and Jayakrishnan crosslinked primaquine with periodate-oxidized gum arabic to form a cross linked gel [100]. In vitro release of primaquine into phosphate buffered saline suggested that the extent of release was dependent on the cross-linking density and drug payload. Cytotoxicity evaluation was performed against L$^{100}$ mouse fibroblasts which suggested that oxidized gum arabic having a degree of oxidation of 50% was mildly cytotoxic at a concentration of 0.025 g/mL [100]. Dandekar et al., prepared hydrogel nanoparticles for loading of curcumin from a combination of hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone. The hydrophilic nature of the formulation was exploited for enhanced absorption and prolonged rapid clearance of curcumin. In vivo anti-malaria studies revealed significant action of the hydrogel nanoparticles when compared to free curcumin control suggesting the formulation is a potential adjunct anti-malarial therapy that can be used along with standard therapy [101].
4. Conclusion

The use of polymer based drug delivery systems provide opportunities for improving the therapeutic efficacy of the presently used antimalarials which are characterized by poor water solubility, drug resistance, instability, poor bioavailability and toxicity. Despite the huge advantages associated with polymer-based drug delivery systems, there is still not enough exploitation of these systems for delivery of antimalarials. There is also very little report on the selectivity of these systems to target parasites. Most the research report so far is laboratory based and as such, there is a pressing need to develop these systems up to the clinical trial stage. Currently some drawbacks associated with some of these systems are low drug loading, high cost of preparation, problem of biodistribution and the interference of the systems with biological system. There is a need for a clear understanding of the mechanism of elimination of these systems. There is also a need to redesign these systems so as to overcome the aforementioned drawbacks. Based on the antimalarial analysis of the polymer-based drug delivery systems from various researcher, it is without doubts that polymer drug delivery systems are potential tools that can overcome drug resistance, reduce toxicity and enhance the therapeutic efficacy of antimalarials. In future, polymer-based drug delivery systems could be employed for the delivery of antimalarials for effective treatment.

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