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Nanotechnology for Improved Anti-Malaria Efficacy; Review Update

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Abstract

Malaria is an infectious disease transmitted by female Anopheles mosquitoes. The main factor that has contributed to the spread of this disease is the increase in the number of drug-resistant parasites. To overcome drug resistance, researchers have developed drug delivery system (nanotechnology) using nanocarriers such as mesoporous Silica and liposomes to encapsulate anti-malarial drug. The drug delivery systems were characterized by distinct features such as good biocompatibility, high percentage drug encapsulation, reduced drug toxicity and targeted drug delivery. In this review article, this drug delivery system developed from nano biomaterials (liposomes and mesoporous silica) for the delivery of antimalarial drugs were highlighted and it was shown that use of liposomes presented some challenges in maintaining its sterility and stability for use and also the fact it possess very short shelf life when in suspension thereby requires additional processes and efforts in making it viable for the market while the four groups of the mesoporous silica used in encapsulating the drugs [MCM-41 encapsulated quinine (MCM-41⊃QN) (1), 3-phenylpropyl silane functionalized MCM-41 loaded QN (pMCM-41⊃QN) (2) MCM-41 encapsulated Atersunate MCM-41⊃ATS) (3) and 3-aminopropyl silane functionalized MCM-41 contained ATS (aMCM-41⊃ATS) (4) also showed improved efficacy however the encapsulation strategy of MCM-41⊃QN (1) stands very effective in delivering the drug to the target cells compared to the delivery by the other mesopourous systems majorly because of the lower cytotoxicity accompanying its functions and therefore, this encapsulated drug may be considered for rational drug design.

Keywords: Malaria; Nanocarriers; Encapsulate; Drug delivery

Introduction

Malaria

Malaria is a mosquito-borne infectious disease of humans and other animals caused by protists (a type of microorganism) of the genus *Plasmodium*. It remains one of the most important disease of public health concern in countries where the transmission of the disease occurs regularly [1]. Malaria is one of the major public health problems in tropical and subtropical countries, Malaria parasites are transmitted from infected host to susceptible host by the bite of an infected *Anopheles* mosquito. As per World the Health Organization's (WHO) Malaria Report 2016, nearly 148-304 million people suffered from acute malaria globally and 0.235-0.639 million among the infected died. Approximately half of the world's population is at risk of being infected by malaria [2]. In 2015, there were 212 million reported cases of malaria and 430,000 malaria deaths worldwide [3]. Over 90% of those deaths occurred in Sub-Saharan Africa. Efforts is being made towards scaling up malaria prevention methods, via greater access to diag nostic testing and treatment, increased use of insecticide-treated bed nets and indoor residual spraying in malaria endemic regions.

Nanoparticles emerge as the future of drug delivery technology as they might be future crucial diagnostic and therapeutic tools [5]. Additionally, one of the major benefits of nanotechnology is the targeted drug delivery at the site of the disease by passive targeting of drugs to the site of action or by selective active targeting of the active pharmaceutic agent [6-7]. Drug delivery nanomediated systems are based on biocompatible nanocarriers, such as gold nanoparticles, carbon nanotubes, nanovesicles, micellar systems and dendrimers [8]. Based on the identified potential of nanoparticles, they have emerged as a promising delivery system for efficient transport and release of antimalarials into diverse cell types as a covalent or non-covalent conjugate to incorporate multiple therapeutic drugs or biomacromolecules [5].

Conventional therapy and drug resistance

There are five major parasite species that cause human malaria: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale Plasmodium Knowlesi* and *Plasmodium malariae* [4]. These parasites pose serious illness, but *P. falciparum* is the most life-threatening of them all. There have been several controls and prevention approaches taken to manage this disease, such as the use of antimalarials. However, the currently used antimalarial drugs have not been found to be effective due to their toxicity, cost and drug resistance [9]. As a result, these factors have resulted in malaria treatment failure [10]. Other factors that contribute to malaria treatment failure include misdiagnosis, poor patient compliance, poor drug quality and incorrect dosing. Due to the aforementioned factors, there is an urgent need to develop drug delivery systems that will be able to reduce the toxicity of the drugs, improve patient compliance and hopefully overcome drug resistance, which is common to the currently used antimalarials [11].

At present, quinine related drugs, Artemisinin derivatives, anti-folates derivatives and new class of combination drugs are extensively used to treat malaria. These drugs are used in combination for better malaria treatment. Quinine related drugs are highly potent in treating malaria. Chloroquine (CQ) has been used for treatment of malaria for over eight decades due to its excellent pharmacokinetic and pharmacological advantages over all other antimalarial drugs. CQ is known for its fast action in blood parasite stages, low toxicity, good bioavailability from oral dosage, water solubility, high volume of distribution in the body and lower cost [12] Primaquine (PQ) is a very toxic drug used in the prophylaxis against all types of malaria. Nevertheless, quinine related drugs are effective against malaria P. falciparum is developing resistance against these classes of drugs. ACT (Artemisinin-based combination therapy) is the frontline treatment against malaria. Artemisinin and its derivatives have the ability to kill a broad range of asexual parasite stages at safe concentrations [12].

In 2005-06, ACTs were deployed as first-line treatment in several endemic countries in Africa, as a result, the malaria cases and deaths were reported to be declining [3]. However, according to WHO via the Global malaria programme (2018), there have been some reports of delayed parasite clearance during routine Therapeutic Efficacy studies of ACTs conducted in Africa. There was also report of high failure rates of ACT along the Thai-Cambodian border [13]. This might be due to the development of possible artemisinin resistance. Moreover, artemisinin derivatives were reported to show dose, time and route dependent neurotoxicity in laboratory animals [14]. Nevertheless, no report is available regarding the toxicity of artemisinin and its derivatives in human. The observed discrepancy between animal and human studies may be due to different routes of administrations [14].

The existing treatment for malaria is taken orally and has three main problems which are:

1. Most antimalarial drugs are broken down in the stomach
2. The drugs have strong side effects
3. The medicine stays in the body for only a short time. These issues have resulted in malaria treatments that were not particularly effective.

Drug delivery and nanotechnology in medicine

Drug delivery refers to approaches, formulations, technologies, and system for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect [14]. Nanotechnology involves the study of the control of matter on an atomic and molecular scale. This molecular level investigation is at a range usually below 100nm. In simple terms, a nanometer is one billionth of a meter and the properties of materials at this atomic or subatomic level differ significantly from properties of the same materials at larger sizes. Although, the initial properties of nanomaterials studied were for its physical, mechanical, electrical, magnetic, chemical and biological applications, recently, attention has been geared towards its pharmaceutical application, especially in the area of drug delivery [14].

Nanocarriers with prolong blood circulation time i.e. stealth nanocarriers have been used for delivering antimalarial drugs in order to increase the resident time in the human body and to increase the probability of drug molecules to interact with infected red blood cells and parasites [6]. In addition to this, nano-drug delivery systems (NDDs) provide protection to unstable drugs, cell adhesion properties, and ability to conjugate specific ligands on their surface. NDDs such as mesoporous silica liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, nanoemulsions are extensively studied for antimalarial drug delivery. However, in this review we will look at efficiency of mesoporous silica and liposomes in as nanocarriers.

Nanocarriers For Antimalarial Drug

Mesoporous silica as nanocarriers nanocarriers for antimalarial drugs

The utilization of mesoporous silica nanoparticles (MSNs) as a strategy in drug design application came as a better alternative nanocarrier due to its inherent noble properties of large surface area, tuneable pore size or volume, high thermal property, nontoxicity, biocompatibility which enables it cargo favorably large drug proportions to the target cells in a controlled kinetic release [15]. Beck et al. [16] were the first to introduce MSN popularly referred to as MCM-41 in 1992. But not until 2001, that Vallet-Regí et al, [17] introduced MCM-41 for the first time as a drug delivery system, and efforts has been devoted to the design of versatile MSNs for treating diverse pathologies. Even though very few studies have been carried out using MSNs as a system for drug delivery in malaria treatment Amolegbe et al. [18] designed MSNs that provided a groundbreaking and very promising approach in the treat-

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ment of malaria. Construction of nano-vector materials, capable of encapsulating antimalarial drugs and delivering them to *Plasmodium*-infected red blood cells (pRBC) with high specificity efficacy and at an affordable cost to the rural man in sub-Sahara Africa is of paramount importance. Urban et al. [19] reported the use of poly (amidoamines) (PAAs) drug conjugates for the delivery of *chloroquine* (CQ) and *primaquine* (PQ) to *P. falciparium* 3D7 *in vitro* with IC50 values of 14.6nM and 2.5μM respectively when the most effective PAA (having an intrinsic ant plasmodial activity, IC50 of 13.7μM was used and to *P. yoelii*17XL *in vivo* with 96.5% reduction in parasitemia at the least dose when the most effective PAA was also used. Movellan et al. [20] constructed nano dendritic polymer drug conjugates for CQ and PQ carriage to *Plasmodium*-infected red blood cell (pRBC) with a clear improvement in the vitro IC50 for CQ and PQ which were 4.0nM and 1.1μM respectively.

Herein the research done by Amolegbe et al. [18] made use of mesoporous Silica in the form of MCM-41 encapsulated quinine (MCM-41⊃QN)(1), 3-phenylpropyl silane functionalized MCM-41 loaded QN (pMCM-41⊃QN) (2), MCM-41 encapsulated Atersunate (MCM-41⊃ATS) [3] and 3-aminopropyl silane functionalized MCM-41 contained ATS (aMCM-41⊃ATS)[4] which were synthesized, well characterized and were screened *in vitro* for their activity against *P. falciparium* W2 strain, cytotoxicity against BGM cells and *in vivo* for their activity against *Plasmodium* berghei The result shows

Antiplasmodial activity and cytotocity of the nanodrugs of MSN

The anti-plasmodial activity and cytotoxicity for the nanodrugs: MCM-41⊃ QN (1) pMCM-41⊃ QN (2), MCM-41⊃ ATS (3) and aMCM-41⊃ ATS (4) show that with the exception of MCM-41 encapsulated ATS, the other three nanoparticle encapsulated antimalarial drugs were active against *P. falciparum* W2 strain and were not toxic against Bufalo, and Green Monkey Kidney (BGM) cells.

Antimalarial activity of nano-silica encapsulated antimalarial drugs

suppressive test using mice revealed that '1' was the most active nanodrug (ED50:< 0.0625mg/kg) against *P. berghei* NK65, exhibiting higher chemo suppression than quinine at a dose two hundred and forty times less than that of QN and also increased the mean survival time (MST) compared to the untreated control. '3' was the second most active against *P. berghei* NK65 (ED50: 0.113mg/kg) and also increased the MST of the infected mice compared to the untreated control. However, it exhibited lower MST in infected mice compared to ATS. The other two nano-drugs were also active; causing more than 50% inhibition of parasite growth. However, as others, the nano-drugs caused the *P. berghei* NK65-infected mice to have lower MST than those administered standard drugs, though increasing MST of the infected mice compared to the untreated control [20].

The results indicated 1 and 3 as the most active nanodrugs, although the latter was inactive *in vitro* this may be due to some modifications undergone *in vivo* of the nanoparticle used for the synthesis of 3 which enhanced the release of the drug from the nanoparticle thereby making the nanodrug to become active. This suggests that MCM-41 was the most effective drug delivery system among the drug delivery systems examined '1' exhibited an ED 50 of <0.0625mg/kg body weight, which was lower than '2'. The results suggest that MCM-41 was able to maintain a steady release of the drug over a long period of time, thereby increasing the half-life of the drug in the blood. This is also evident from the *in vitro* dissolution experiment carried out. In like manner, '3' exhibited lower ED50 than aMCM-41 encapsulated ATS, still emphasizing the fact that MCM-41 is effective at steady release of its drug compared to other nanoparticles. This also suggests that the framework of MCM-41 was effective in allowing the nanodrug to get adsorbed to the infected red blood cells [21].

MCM-41 encapsulated QN (1) with a controlled release was the most active of all the four nanodrugs evaluated, causing higher inhibition of parasite growth than the parent drug and exhibiting a mean survival time favorably compares with that of parent drug. The results, therefore, suggest that '1' is more effective drug delivery system compared to other nanoparticles used in this study. Thus, its application as a drug delivery system for the antimalarials makes it a suitable candidate for the next generation active nano drugs malariotherapy products [12].

Moreover, MCM-41 enhanced a dose of 0.0625mg/kg body weight of QN (which is 240-fold less than 15mg/kg body weight of the unencapsulated QN used in this study) to cause a higher inhibition of parasite growth compared to the unencapsulated drug. In the same vein, MCM-41 enhanced a dose of 0.25mg/kg body weight of ATS (which is 20-fold less than the 5mg/kg body weight of the unencapsulated ATS used in this study) and interestingly still to cause a higher inhibition of parasite growth compared to the parent drug. This result, however, concur's with the high intracellular uptake property of MSN [15]. The magnitude of the reduction in the amount of drug needed to cause higher inhibition in parasite growth than the unencapsulated drugs was higher in MCM-41, suggesting that MCM-41 further enhanced its effectiveness in drug delivery.

The nanodrugs increased the mean survival time of the infected mice compared to that of the untreated control. However, the reduced mean survival time observed in mice treated with various mesoporous silica nanoparticles loaded with antimalarials, except MCM-41 encapsulated quinine, compared to those treated with parent drugs suggests some level of toxicity. The nanodrugs were not toxic against Bufalo Green Monkey Kidney cell line *in vitro* (MLD50:>1000). Thus, the cause of the reduced MST observed *in vivo* is a subject for further studies. The results corroborate previous reports that unfunctionalized nanoparticles (e.g. MCM-41) are well tolerated [22]. MCM-41 encapsulated QN had comparable

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mean survival time to that of QN, even exhibiting higher mean survival time than quinine at some doses which were much less than that of unencapsulated quinine.

Challenges of Mesoporous Silica as drug delivery system

Some MSNs design proffer cytotoxicity in the course of delivering treatments as shown in the study by Amolegbe et al. [18] where MCM-41⊃ATS (Artesunate encapsulated with MCM-41 MSN) shows cytotoxicity in kidney cell lines. This result further validates the work done by Di Pasqua Anthony, et al. [23] which measures the cytotoxicity of MCM-41, two of its functionalized analogs, AP-T (grafted aminopropyl group) and MP-T (mercaptopropyl groups) and Spherical silica nanoparticles (SiO(2)) towards human neoroblastoma cells and the results shows that on a particle basis, MCM-41 is the most cytotoxic material among the mesoporous silica material used. In some other studies the use of Mesoporous Silica (MS-Ap-PAMP adjuvants) in tumor immunotherapy indicates maximum *in vitro* immunogenic activity [24]. So therefore, mesoporous material like the MCM-41⊃ATS indicates some form of cytotoxity in its delivery of antimalarial drug and also other therapy using mesoporous materials indicated immunogenic activities [23].

Liposomes as nanocarrier for antimalarial drugs

According to Farouk et al. [25] Liposomes are small and artificial spherical shape vesicles that can be created from natural non-toxic phospholipids and cholesterol. Due to their size and hydrophilic and hydrophobic characters in addition to biocompatibility, the liposomes are considered as promising systems for drugs delivery [27]. Generally, liposomes are definite as spherical vesicles with particle sizes ranging from 30 nm to several micrometers. They consist of one or more lipid bilayers surrounding aqueous units, where the polar head groups are oriented in the pathway of the interior and exterior aqueous phases [27]. Liposomes are extensively used as carriers for numerous molecules in pharmaceutical and cosmetic industries. Additionally, food and farming industries have extensively studied the uses of liposomes encapsulation to grow delivery system that can entrap unstable compound such as antioxidant, antimicrobials, flavors and bioactive elements and as well shield their functionality [27]. Liposomes can trap both hydrophilic and hydrophobic compound, avoid decomposition of the entrapped combinations, and release the entrapped at designated targets [28]. Because of their biodegradability, low toxicity biocompatibility and aptitude to trap both hydrophilic and lipophilic drugs [29] and simplify site specific drug delivery to tumor tissue Hofheinz et al. [30] liposomes have increased rate both as an investigational system and commercially as a drug-delivery system. Many studies have been conducted on liposomes with the aim decreasing drug toxicity and targeting specific cells [29] Liposomes are synthetic structures that consisted of several hundred nanometers in diameter containing one or several phospholipid bilayers enclosing an aqueous core [31].

The concept of utilizing liposomes as vehicle for drug delivery system was introduced in 1970s and more recently the use of liposomes nanocarriers has been extended to immunological adjuvants and as delivery vehicles for vaccine especially to specific target cells [32]. Both lipophilic and hydrophilic particles can be incorporated into liposomes and delivered to target sites within the host organism. Hydrophilic particles including peptides, proteins and nucleic acid can be entrapped within the inner aqueous phase while lipophilic drugs such as adjuvants and lipopeptides can be incorporated onto the outer phospholipid layer. Liposomes are immunologically advantageous due to their targeting and uptake by professional antigen presenting cells, and additionally antigens, adjuvants and antibodies can be attached to the outer surface of liposomes to facilitate delivery into infected cells [32]. Optimal combinations of antigens, antibodies and adjuvants give liposomes plasticity and allow the opportunity for optimization of different drug regimens. Liposomes have shown significant effect as nanocarrier for the prophylaxis and also for the treatment of malaria and as well as for vaccine delivery for the prevention of malaria [33]. Currently, effective therapy for malaria is limited due to toxic drug side effects and the development of resistance to current drug regimens. Encapsulation of therapeutic agents within liposomes can favorably alter the dose and distribution of drugs within the body, which may significantly reduce unwanted toxic side effects, increase treatment efficacy and reduce the risk of drug resistance [34]. Presently, malaria vaccine strategies suffer from the problem of resistance to recombinant antigens and as well the need for frequent re-boosting. The use of live-attenuated parasites is limited mainly because high doses of *Plasmodium* are needed and because a clinically appropriate route for inoculation has not been found [35].

Current therapeutic administration strategies release free drugs into the blood and offer little specificity regarding infected cells [25]. Early studies have indicated that the liposomalization of the antimalarial agent chloroquine increases its maximal tolerable dose and its efficiency and activity against murine malarial infections greater than just chloroquine alone [25] Moreover, the ability to increase the doses of chloroquine per injection after liposome encapsulation allowed successful treatment of infection with chloroquine resistant *P. berghei* which could be cured by a seven-day course with the maximum tolerable dose of free chloroquine [36]. More recently, antibody coated liposomes loaded with antimalarial drugs such as primaquine and chloroquine completely arrested human infecting parasite, *P. falciparum* growth *in vitro* and cleared infections [37]. This success was attributed to dual therapeutic and prophylactic effect achieved with the use of liposome vesicles targets to both infected and non-infected erythrocytes [37].

Resistance to current antimalarial therapy is attributed to a large genetic diversity of *Plasmodium* strain, specific mutation in *P. falciparum* chloroquine transporter gene and multi drug resistance genes in *P. falciparum* [39]. Liposomes circumvent drug resistant malaria because they are targeted for intracellular de-

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livery which bypasses chloroquine transponder and pass through cell membrane by alternative mechanisms such as membrane fusion or entrapment of chloroquine in pH-sensitive liposomes [36]. Directing liposomes to parasite-infected erythrocytes is another strategy that would allow for selective drug distribution and allow for exposure of lethal doses directly to the pathogens [39]. Ligands conjugated to the surface of liposomes can be used to target and specifically bind *Plasmodium* infected cell [19]. Because the blood-stage of *Plasmodium* infection is responsible for all symptoms and pathologies of malaria, *Plasmodium* -infected erythrocytes are the main antimalarial therapeutic target. The targeting of liposomes to erythrocytes using heparin and monoclonal antibodies to erythrocyte surface proteins have been studied *in vitro* and have shown promise towards targeted drug delivery. Marques et al. Encapsulated primaquine in heparin-coated liposomes, this formulation was demonstrated to have antimalarial activity and specific binding affinity for *Plasmodium*-infected erythrocytes *in vitro* via heparin targeting of heparin-binding proteins in erythrocyte membranes. Antibody-mediated erythrocytes targeting using liposomes are another promising strategy for targeted drug release. Recently, drugs carried by liposomes were shown to be specifically targeted *in vitro* to *P. falciparum* infected erythrocytes relative to noninfected erythrocytes likely by docking to infected cell surfaces to facilitate membrane fusion [40]. This demonstrates the feasibility of constructing a carrier able to completely discriminate infected from non-infected erythrocytes.

Challenges of liposomes assisted drug delivery for malaria

In most cases liposomal formulations are nontoxic, but certain formulations such as the cationic formulations tend to be cytotoxic. This is especially true when liposomal doses are very high [19]. The sterilisation of liposomes is a complicated conundrum, as liposomes are sensitive to high temperatures, as well as certain methods of radiation. Sterilising with chemicals is not a viable option either, as it may affect the stability of the liposomes. The only method for creating sterile liposomes is by filtering the liposomes through a 0.22μm membrane filter after production. This method is only suitable if the liposomes are smaller than 0.2μm in diameter. This method does not remove viruses [41]. Another option is filtering the initial solutions through 0.45μm regenerated cellulose filters and glass fibre filters before starting production, thereafter the entire production process must be done under aseptic conditions [42]. For a pharmaceutical product to be viable for the market, it requires the product to be stable in some form or another for at least a year and a half to two years. To achieve this with liposomes is very difficult if the liposomes remain in suspension. Other methods may be used to increase the shelf life of liposomes, such as freeze-drying after production [41-45]. Two factors play a major role in the stability of liposomes namely, chemical and physical degradation. The chemical degradation of liposomes is attributed to oxidation and hydrolysis. Physical degradation is most often attributed to the difference in the packing density of the lipids in the bilayer structure. Physical degradation is also a huge factor when formulations are freezedried. When products are freeze-dried a so called cryoprotector must be added to ensure the product is stable when reconstituted [25].

Conclusion

Malaria is a disease that been affecting the people from tropical and subtropical countries. But, the recent development in nanomedicine is opening up new possibilities and is providing better and effective solutions in treating this complex disease (malaria). In this review, the use of Mesoporous Silica and Liposomes as Nanocarriers nanocarriers for antimalarial drugs has shown to provide more efficient and fast delivery of the antimalarial therapy to the targeted cells without the complications accompanied by other routes of delivery thereby making them safer. However, use of liposomes has presented some challenges in maintaining it sterility and stability for use and also the fact it possesses very short shelf life when in suspension thereby requires additional processes and efforts in making it viable for the market. In other hand the Four groups of Mesoporous Silica used: MCM-41⊃QN (1) pMCM-41⊃ QN (2), MCM-41⊃ ATS (3) and aMCM-41⊃ATS (4) showed better efficacy however the encapsulation strategy of MCM-41⊃QN (1) stands very useful and effective in delivering the drug to the target cells compared to other delivery of the mesopourous systems majorly because of the lower cytotoxicity accompanying its functions and therefore, this encapsulated drug may be considered for rational drug design.

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