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NANOCARRIERS FOR THE DELIVERY OF ANTIMALARIAL DRUGS

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ABSTRACT

Malaria is a non-contiguous disease caused by a protozoon which spreads through female anopheles' mosquito (Malaria mosquito) generally found in temporary rain pools. According to the study world's half populace is at danger of being infected by malaria. The main agent that has been involved for the spread of this infection is increasing in the number of drug resistant parasite. Therefore, to overcome from these problems bio-nanotechnology drug delivery systems have been developed to make easy at particular site or where we have to target our drug and hence reducing the development of resistance and toxicity issues related to drug dependency.

KEYWORDS: Malaria; Drug-Resistance; Nanotechnology.

INTRODUCTION

Malaria is a disease caused by a Plasmodium parasite which remains a health issue.[1] It is a waste that is transmitted to from mosquitoes to human beings. The Anopheles (female) mosquito is answerable for the spread of malaria to the human being. Five kinds of Plasmodiums that can pass infection to humans are- Plasmodium falciparum, Malaria parasite *P. vivax, Quartan malaria, Plasmodium ovale, Plasmodium Knowlesi*.[2] Most cases of death are found in newborn babies, gestation and peoples suffering from HIV/AIDS. Almost half of the world's population is at danger of suffering from malaria.[3] WHO 2018 report shows that, 40% of malaria cases have been reduced.[4]

According to WHO 200 million patients were listed as suffering from malaria in 2018 report, out of these 3.5 million malaria cases related to African countries.[5]

Malaria Parasite life cycle

The life cycle involves between two hosts such as mosquitoes to humans and humans, it finds only human hosts, as living organisms.[6] It infects humans, liver cells and matures into schizonts.[7] The phase of malarial parasite is separated into two consecutive stages: (a) sexually transmitted, continuous then progressively within the organism and (b) through the sex stages, beginning within living organisms and ending within female mosquitoes.[6] The life cycle of malaria is shown in Figure 1.

Stage of infection (sexual reproduction)

Infected mosquito bites, injects plasmodium parasite (sporozoites) into the blood stream of living organism.[8] Sporozoites make the entery to liver with the help of kupffer cells. After penetrating the liver cells, they divided and rupture liver cells that help produce new parasites. This kind of isolation is called as schizogony and life cycle called as merozoites.[7]

Asexual (Erythrocytic) phase

Parasites are transported to liver cells or reproduce asexually generally form merozoites in 7-10 days. Without manifestation of any symptoms, they occur.[9] Merozoites attacks red blood cells multiply and rupture cells by entering through blood streams. After repetitions of cycle, it shows symptoms like as fever, and headache. A number of the merozoites reproduce asexually to form new merozoites.[9] These merozoites spread into the blood.[10]

Sporogonic cycle

Gametocytes generally picked up by the mosquito after anopheles' mosquito (Malaria mosquito) bites an infected person. In the abdominal wall of mosquito, zygote is formed by gametocytes. The zygote grows into ookinete. Then it is converted into a replica oocyst to form sporozoites in the outer part of mosquitoes stomach. Within oocyst, sporozoites divided and explode, thus in the salivary glands thousand of sporozoites travel. If infected mosquito bites another person, human infection life cycle begins.[11,12]

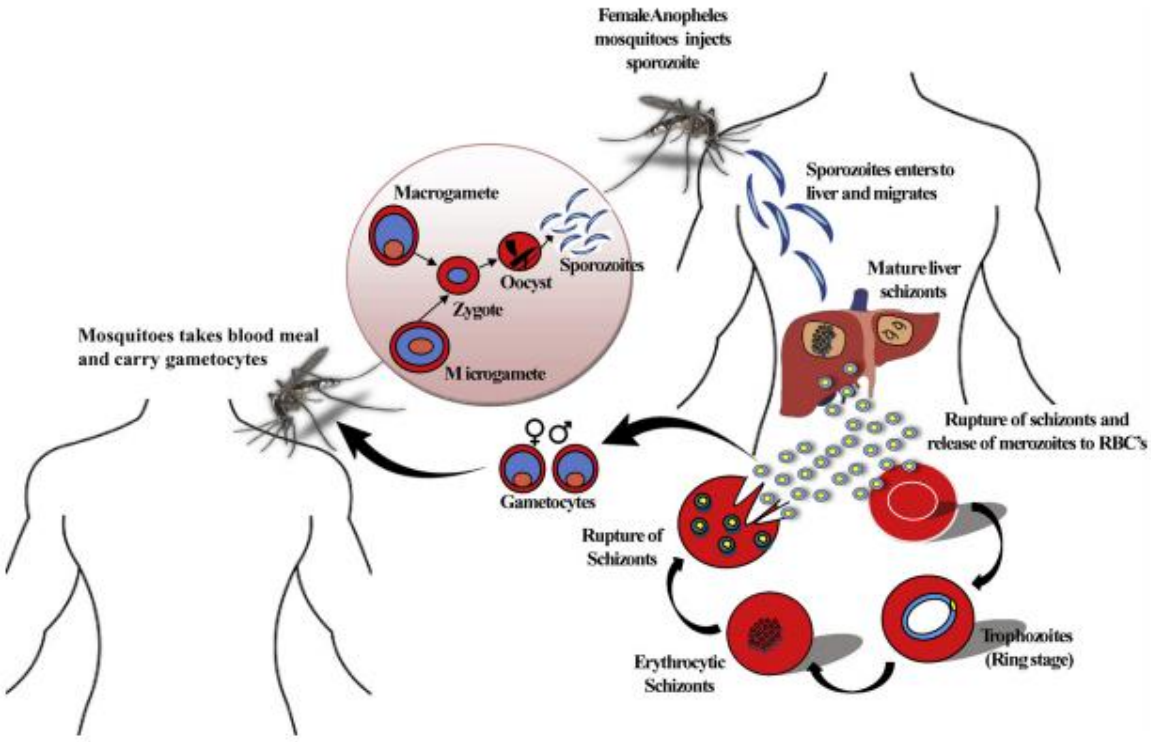

Figure 1: Life cycle of Malaria.[7]

Existing anti-malarial drugs

Currently available Antibiotics are generally used for the prevention and cure of malaria infections. Many anti-malarial medicines refer to the stage of infection that is erythrocytic stage, that stage is known to be the stage of causing illness showing symptoms. Various programs such as the malaria control campaign and others, designed to control the disease, have gained significant benefits in few areas of the world, but rather than that of these precautions malaria still infects large number of peoples and killing millions of people every year and remains a life-threatening disease.[13]

Current anti-malarial drugs are divided into four categories, including Quinolines, Antifolates, Artemisinin, and sulfadoxin.[14]

Resistance to anti-malarial drugs

Resistant of drug is caused by *P. Falciparum*; it causes high temperature or anemia which causes millions of deaths every year.[15] Resistance to antibiotics starts when parasites survive also increase in the amount of a given drug; it often kills as well as secures its recurrence.[16] Several factors contribute to the spread of resistance of drug. These parts may include costly treatment, drug overdose, adverse reactions and patient adherence.[17] The antimalarial resistance mechanism is complex, varied and influenced by many genes.[18]

The occurrence of resistance to malarial parasites is due to genome and genetic bases, has been explained as abnormal, high adaptable, or highly plasticized.[19] However, the exact mechanisms underlying the development of resistance are not yet clear. Initially, it was thought that a substance called multidrug resistance (Ability of an insect repellent to develop a drug resistant clone under pressure) is related with improved resistance, a certain type of *P. Falciparum* and is elevated to a elevated frequency of 1000 × to improve resistance to particular substance.[20]

Antimicrobial resistance mechanisms of malaria are even more unique, for the insect is able to counteract the specific resistance to the drug's cells. This may cause occurrence to another diseases, e.g. tuberculosis infection, in which the phenotypic drug resistance is largely driven by the development and 'nonspecific' drug efflux through the introduction of multidrug-based drug (MDR) and is observe a major cause in developing drug resistance. Despite the fact this insect uses carriers (MDR), to means of drug resistance to different classes of antimalarials, they are non the main sources for development of resistance and MDR causes only a problem in specific pockets of regional.[21]

Table 1: Antimalarials drugs, mode of action, limitations and dosage forms.[22,23,24,25]

Drug	Mode of action	limitations	Dosage
Chloroquine Phosphate	Intraerythrocytic trophozoites contains acidic Food vacuoles, chloroquine accumulates with food vacuoles and prevent degradation of haemoglobin.	Development of resistance throught the world	tablets
Primaquine phosphate	During respiration process it intereferes with electron transport in parasite.	It causes hemolysis in glucose 6 phosphate dehydrogenase in deficient patients	tablets
Quinine sulfate	Accumulation of cytotoxic heme within the parasite after it acts on heme detoxification pathway	Cause cinchonism, hypoglycaemia, serious, hematologic disorders.	IV, IM
Mefloquine Tablets	It acts by forming complexes with free heme which is toxic for the parasites.	Cause severe neuropsychiatric reactions, long half life	tablets
Dihydroartemisinin	Acts as a gametocytocidal and schizontocidal.	Very short half-life.	tablets
Atovaquone	It acts by blocking the electron transfer chain that is present inside the parasite.	Absorption is very poor and variable and half life of drug is long elimination	tablets

The need for nanotechnology

Nanotechnology program, an innovative way to deliver medicine through its use in science and technology in a very interesting way. This technology has been giving tools that allow

conversion of structural to synthetic reactions, as well as chemical reactions, giving them with the most useful and specific selection. By abusing the nanocarriers that can be used to develop a drug specifically targeted to protect and protect the drug or immunosuppressive agent, improve the substance according to its intended purpose, reduce the frequency of dosage, modify biopharmaceutics and pharmaceutical properties thus overcome the side effects and thus drug efficacy.[26]

The main goals of nanotechnology based malaria treatment toward bring the drug treated in the vacuoles vacuum of intracellular parasites or expand the storage of drug into the blood. Also increase in the time of drug in blood stream; it also helps in contact including red cells that are affected and the membrane of parasites.[27]

For drug delivery nanocarriers in the stages of malaria

Polyamidoamines nanoparticles as nanocarriers

PAAs are belonging to group of polymers that decompose and reassemble easily. The procedure for preparation of PAA's is quite simple, friendly to the environment and simply distributed, so it is suitable for sale in low-income districts per person. These structures obtained the current amino and amido group arranged usually in the major sequence, due to the non absence of extra acid or low-density essential materials supported by polymeric particles that can be classified as polyelectrolytes.[28]

While some Polyamidoamines are occupied by the kidneys or liver immediately after giving injections intravenously, others can flow in the blood for a longer time, indicating a tendency to get abscesses due to the firming effect.[29] This longevity of blood vessels is necessary factor to examine when picking out candidates for drug delivery systems, as increase in circulation will transmit the interaction of polymers with the target cell that puts them inside engulfing process of cell.[30]

The properties of PAA, ISA1 and ISA23 have been verified for, secretion or direct supply of anti-malarial drugs mentioned.[31]

In polyaddition of agmatine with acrylamido acetic acid AGMA1 is found and contains different groups like guanidine, tert-amine or carboxyl group. In delivery of intracellular nucleic acid these polymers have been recognised or reported as vectors[32], while in study for delivery of proteins and anti cancer drugs carrier ISA1 and ISA23 were useful.[33]

ISA23 has specifically 1 been shown to be given properties such as immunosuppression without the selective concentration of the liver, while a large proportion of AGMA1 has been shown to be localized hepatic after-injected in mices.[29] PH decreases to 6.5 in endosomes and after 5.0 lysosomes, polyamidoamines turn into more cationic and exhibit properties of endosomolytic in intracellular segments.[34]

Polyamidoamines targets to different AGMA1 and plasmodiums species has significant antimalarial activity, demonstrating combining to merozoites or possibly inhibiting their entry of red blood cells. Exposure to antibodies to the immune may be used in development of new malarial vaccines in which Polyamidoamine may act a key role as carriers for antiretroviral vaccine supplements.[35]

Nanocarriers based on Polymer

Nanoparticle polymers that are collected from non-volatile unaffected polymers such as chitosan, gelatine, albumin, and poly-made polymers like polyacrylamide, lactic-co-glycolic acid, etc. In comparison to its repair or storage conditions Polymeric nanoparticle has a high density of biological fluid which makes them more attractive as compared to other systems of drug delivery.[36] Polymer nanocarriers has many benefits such as improve biocompatibility, decreased toxicity, improved drug availability, reduced patient compliance, increased drug resistance and drug overdose.[37] Nanoliposomes, micelles, Hydrogels, dendrimers and polymer-drug conjugates etc. are different types of systems made for antimalarials drugs delivery.[37]

Hydrogels

These are three dimensional polymeric network made up of synthetic polymers and natural polymers. These can absorb or store huge amount of water and organic fluid.[38] They are inexpensive, non toxic, incompatible, environmental friendly for e.g. there temperature, pH or electric field and also minimise the speed of drug release.[39] Aderibigbe (scientist) make hydrogel by taking gum acacia. They mixed hydrogel with curcumin and 4-aminoquinoline. Results of invitro elevated the long and continuous extraction of curcumin, while 4 aminoquinoline showed temporary release at 37◦C. A major feature that influenced the release of drugs is found to be the degree of connection with hydrogel. In addition, initial studies have proposed that hydrogels may be used as a two-pronged approach to drug delivery with antimalarials with different pharmacokinetics.[40]

Aderibigbe and Mhlatika prepare protein (soy) split carbopol and polyacrylamide-based gel into chloroquine diphosphate and curcumin. These were pH-sensitive. In-vitro extraction of these drugs from hydrogels was tested. Method for curcumin extraction is slow and stable as compare to chloroquine. Hydrogels may be used in the delivery of two or more anti-malarial drugs these results suggest this.[41] Musabayana designed for pectin hydrogel patch for delivery of chloroquine, to mask there bitter taste.[42] In-vivo studies in mice showed that use of a drug filled component can increased the release of Na^+ in comparison to mice in which intravenously administration of drug in the postoperative period of animals. This shows continuous releasing of residual chloroquine. The results indicate, chloroquine administration using hydrogel can transmit patient compliance.[42]

Nano biomolecule (Dendrimers)

These are three-dimensional and tree shaped monodispersed nano-biomolecule that exhibit more water solubility and a specific molecule weight that emerges as a suitable carrier for drug. These are made up of three main elements: the central-core, the inner-branches, and the outer boundary groups. Drug molecules are inserted into the internal area to improve performance of drug, reduction in drug toxicity and the drug release is controlled. Many dendrimers have size of n10 nm as a normal width.[43] P. Agrawal, Polyethyleneglycol composed of dendrimers of chloroquine phosphate, bound without having L-lysine. Wearing it showed a profile that drug release is controlled, showing reduction in haemolytic toxicity and less immunogenic than uncontrolled formation.[44]

Badra et al. synthetic dendrimers of polypropylenimine (PPI) mixed with galactose delivery of primaquine phosphate to cells of liver. Michael prepared the formulation for hydrogenation response. In-vivo results show that galactose-binding dendrimers were increases the drug injection effectiveness. The release of in vitro drugs was maintained for 5 to 6 days and on the basis of result obtained haemolytic toxicity; BP studies indicate that the formulation prepared is not dangerous and appropriate for the continuous supply of primaquine to the liver cells.[45]

Liposomes

Liposomes are a phospholipid vesicular unit illuminated in varying sizes from 80-100 nm; it can include compounds lipophilic and hydrophilic. Properties of liposomes vary in lipid composition, size, and preparation process and can be used according to specific requirements.[46] It can be used to combine both the compounds. Drug delivery systems of

liposome has benefit of less toxic, also has protection against chemical damage.[47] Eggs of phosphatidylcholine and cholesterol used in the composition of neutral liposomes were proposed to be the first antimalarials nanocarriers.[48]

Vinoth Rajendran reported that the monensin in PEGylated stearyl amine liposomes has curative activity against malaria. Composition of this may be more efficient compared to alone monensin in strain of Plasmodium falciparum but monensin to long-acting liposomes and free Artemisinin has led to an increase in mortality of parasites and to protect its survival.[49]

Efforts were made in recent studies to design liposomes composed of phosphatidylcholine; PE; CHOL and 1,2- dioleoyl-sn-glycero-3-phosphatidylcholine used a thin film hydration method for the effective delivery of drugs to damaged RBCs by increasing availability of drug and exposure. It consist of probes of fluorescent pyranine , Carboxyl quantum-dots ,CQ which are combined with certain half antibodies for identification of the P. falciparum form containing pRBCs with an active target identification virus. Immuno-liposomes have a size of nearly about 200 nm and can able to deliver the drugs directly to the pRBCs, during incubation for 90 minutes. Less amount of cohesion were seen in liposomal lacking antibodies as compared to immunoliposomes. They observed that IC50 value of the drug CQ is ten times lower as compared to the standard solution with immunoliposomes.[50]

Silver nanoparticles fight malaria

A derivative of silver and silver has long been used in the treatment of different infectious diseases from ancient times. For the treatment of contagious disease Silver nitrate and silver sulfadiazine is widely used until the mid 20th. Toxins of silver are used against microorganisms and can be used in methods that are gradually revealed, and different from the process of other metallic drugs: i) distraction of cell wall integrity and impairment of cellular cell function; ii) dysfunction of cell metabolism due to enzyme deficiency, protein denaturation, inhibition of bacterial respiration; iii) bacterial DNA damage and RNA, including replication processes.[51]

Most recent study of silver-based antiplasmodial drugs from Hemmert (2013), prepared for a series of mono- and dinuclear silver structures containing mono- and bis based ligands, all N-working groups like (i) -amide, alcohol, and nitrogen containing heterocyles quinoline and

bipyridine, and tested with chloroquine-resistant type P. falciparum. Anti-bacterials and antifungals are of same species containing carbenes.[52]

Recent research has shown that the synthesis of metal nanoparticles has a wide range of uses in the field of biomedical due to their unique physical properties Of all metals, silver nanoparticles are widely entertain due to their broad antibacterial activity.[53] It is also state that to release of silver ions, which are closely related with the thiol and phosphate groups present in the enzymes and DNA of viruses and proteins.[54] The behavioral changes state that binding of AgNPs to membrane or DNA stop the bacterial cell from showing important functions such as respiration and replication which cuases death of the cell.[55]

Lipid solid nanoparticles (SLNs)

These are colloidal carriers that contain triglycerides, complex compounds of glyceride, solid fats and sometimes solid waxes also at room temperature and the body. These are naturally stable, preventing drug degradation, biological incompatibility and degradation problems and are more expensive compared to phospholipids and decaying polymers.[56] Hydrophobic substance is trapped within a hard matrix that strengthens release of drug and prevents premature degeneration.[57]

Transferrin that is conjugated solid lipid nanoparticles were invented for their power to identify Quinine dihydrochloride in malaria control regimens.[58] Quinine loaded Tf-SLNs are manufactured by ethanol using hydrogenated soya phosphatidylcholine, CHOL, triolein, and DSPE. In-vitro fluorescence examination have shown improved detection of Tf-SLNs in brain tissue as compared to unrelated SLNs. In-vivo studies tested Quinine plasma levels and distribution of tissue after administration intravenously of Quinine loaded Tf-SLNs with unplanned Quinine and SLNs in comparison to those of free drugs. Intravenously administration of Quinine dihydrochloride solution has result in higher concentrations of drug in serum as compared to SLNs. The combination of Tf unique improved brain Quinine capture, which is demonstrated by the acquisition of high percentage of brain volume following the administered of Tfcoupled compared to standard drug solution or SNLs.[59]

J.O. Muga et al., states that heparin composed of strong lipid nanoparticles combined with Chloroquine and non-heparin functionalized SLNs. performances showed higher antiplasmodial in-vitro activity against CL sensitive (D6) and CL-resistant type W2 with free CQ. Effect seen of lipo nanoparticles contains lipid nanoparticles when the cab having

positive effect, includes the ability to target directly to the disabled RBCs. Therefore they suggest that Anti-malarial activities compared to conventional free drugs should be improved by nano based drug delivery system.[60]

Nanoemulsions or Microemulsions

Nanoemulsions are thermodynamically stable liquid-in-liquid dispersions, meaning O / W emulsions that are fortified with surfactant in the form of small droplets having a diameter of 0.1–100 mm. Nanoemulsions have such useful things that they are not expensive, long-lasting and available as oral scale forms.[61] These have a uses as drug delivery carriers that include increase drug load, strengthening drug availability, increasing drug availability, reducing variability of patient, controlling the release drug and protect against damage of enzyme.

Automatic delivery was increased by PB. Memvanga et al., of the oral administration of β-arteether. The making showed no intestinal Caco-2 cell toxicity and increase performance compared to P.berghei with a daily dose of 24mg per kg for four days of 100% survival in rat rats at 42days. They also concluded that lipid based drug delivery is a granted treatment for malaria through administration by an artisan.[62]

In other study of NanOsorbARM is developed to detect its activity of antimalaria in opposition of infected Plasmodium berghei mice. NanOsorb ARM has shown superior activity of antimalaria in comparison to commercially constructed ARM (LaritherVR). The authors found that the placebo showed higher activity compared to LaritherVR indicating the active ingredients, i.e. Gelucire-44 / 14VR, LabrasolVR and Capmul opted in the NanOsorb formulation may have antimalarial activity.[63]

Y Yang et al, has developed lipid based emulsions that have been given intravenously in the combination of Artemether and Lumefantrine, made with a high infusion and strength. High concentration of Cmax is observed in mice in a study to manufactured composition with vascular solution. Given activity examine important jump in the complex research of malaria.[64]

Nanocapsule

These can be explained as a submicroscopic colloidal carrier consisting of an oil type spine or water core rounded by a thin layer of polymer which have bioactive compounds that is

generally incorporated internally for protection from factors like heat ,oxygen, light, also its stability increases and improves , availability of nano compounds that are encapsulated.[65]

Anand et al., he found the natural protein lactoferrin in addition to its nanoformulation made up of alginate enclosed, buffalo calcium phosphate for active installation against rodent parasite P. berghei. Formulation made in implants reduced the viral pressure and also altered mRNA sequences in mice. In result, they find a combined inhibition and controlled positive effect of metabolism.[66]

Velasques et al., thoughtfully he study that the combination of QN and Curcumin in the nanocapsules of polycaprolactone. Coating of polymer is done to stop the instability of the ultraviolet trigger QN and curcumin. Also combination of 2 drugs in 1 nanocapsule enhances the affect of anti-malarial in opposition of W2 complications with 3D7 P.Falciparum. How much toxic was also studied in Caenorhabditis elegance showing nanocapsules loaded with Quinine + curcumin that reduced toxicity in comparison to free drugs.[67]

CONCLUSION

In above mentioned review article, we have tried to report the chances in the progress of new ways of different ways to treat or control malaria by improving the limitations relates with the available drug moieties such as toxicity of drug, substandard solubility, defective drug loading, chemical nonuniformity, occurrence of resistance. At present, many of the work that has been done is laboratory work and still there is a need to do a clinical trials. According to research based upon in-vivo and in-vitro studies it has been clear that nanocarriers used in drug delivery systems are favourable candidates that can increase the therapeutic effectiveness of antimalarials, decrease the toxicity and get the better of drug resistance.

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