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Review:

An Overview of Application of Nanotechnology in Malaria Control

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Abstract: Infectious diseases caused by parasites are of immense global significance as about 30% of world's population experiences parasitic infections. malaria is the most life threatening disease and accounts for one to two million deaths round the globe every year. Currently, there is no available effective vaccine against malaria. The shortcomings of malaria preventive and curative drug treatments have become a major reason for the failure to eradicate the disease. There is an urgent need for an effective antimalarial agent due to increasing drug resistance of Plasmodium falciparum. Nanotechnology has been identified as the new frontier in the fight against this disease. Nanomedicine is a new technology utilizing nanometer scale drug delivery systems as therapeutics, able to confer advantages which include improved drug pharmacokinetic profiles, organ, cell and parasite targeted drug delivery, reduce doses and reduction in drug toxicity. Nanomedicine can address the challenges associated with current anti-malarial drugs by reformulating the drugs in nanomedicine drug delivery systems (NMDDS). The development of these particulate carriers as vehicles for delivery of active compounds is a novel area of research that provides a new hope in malarial chemotherapy.
Key Words: Malaria, treatment, nanotechnology, nanomedicine drug delivery systems

Introduction:
Malaria is a fatal parasitic disease caused by Plasmodium species. In humans, the disease is due to *Plasmodium falciparum, P. vivax, P. ovale, P. malariae,* or *P. knowlesi*. Infection is spread by a vector of these parasites; the female Anopheles mosquito. It can also be transmitted from an infected mother to a child in the womb, through blood transfusions and organ transplants.[1] Malaria thrives in tropical and subtropical regions. This is due to the favourable weather and environmental conditions of this region. The World Health Organization estimates that in 2013 there were almost 200 million cases malaria and more than 500,000 deaths.[2] *P. falciparum* is the major causative agent of malaria in this region. The high incidence of infection is due, in part, to the lack of effective control of the Anopheles vectors. Vector control techniques including insecticide-treated mosquito nets (ITNs) and indoor spraying with residual insecticides (IRS) have been used as preventive measures to help control outbreaks of malaria, especially, in countries with a high rates of malaria contraction such as in Africa south of the Sahara. Indoor spraying is most efficacious when at least 80% of the houses in an area are treated. The disadvantage of indoor spraying is that the treatment must be repeated several times a year. Genetically engineered mosquitoes that are resistant to colonization by the malaria parasite have been produced using transposons and P elements approaches.[3] Additionally, the evolution of multi-resistant *Plasmodium parasite* to most of the available drugs such as chloroquine, pyrimethamine, aretesunate, sulfadoxine, etc, have resulted in increasing cases of this disease, therefore the development of alternative effective antimalarial agent is needed.[4] The World Health Organization has recommended a combination of anti-malarials and artesunate to treat uncomplicated malaria cases. An endemicity is possible if malaria builds resistance to these drug combinations sentence not clear.[3]
Currently, most of the drugs used in treating malaria have low bioavailability and adverse side effects. This adds to the need for new prophylaxis and therapeutics.[4] Considering the small number of new drugs or innovative antimalarial medicines approved since 1990, the search for more efficient and less toxic antimalarials, the development of a successful vaccine, and the design of nanotechnology-based delivery systems applied to drugs and antigens are likely to be the main

strategies in combating this disease.[2] Nanoparticles are particulate dispersions or solid colloidal structures ranging from 1 - 1000 nm in diameter.[5] They are composed of synthetic, semi-synthetic and natural polymers in which active therapeutic molecules have the capability of being entrapped, encapsulated, dissolved, absorbed, or chemically attached.[5,6] Due to their biodegradability, biocompatibility, and versatility in application, natural hydrophilic polymers have also been extensively investigated.[7,8] Natural polymers are classified as proteins (gelatin, albumin, lectin, legumin, and vicillin) and polysaccharides (alginate, dextran, pullulan, and chitosan).

Nano carriers play an important role in improving the pharmacokinetic profile of effective drugs which due to poor water solubility, low bioavailability and high toxicity which limit their use in pharmaco- therapy. [9.10] Nano carriers have been proposed for malaria diagnosis [11,12] treatment [13-15] and vaccine formulation.[16,17] The resistance of malaria parasites to drugs may also be due to the use of inadequate pharmaceutical dosage forms of antimalarials. Nanotechnology systems may play a crucial role by targeting drugs specifically to their site of action.[18] Furthermore, banned toxic drugs can now be used as a result of nanotechnology by modifying their biodistribution and reducing toxicity.[13] This is of advantage in malaria therapy, since there is a dare need to deliver drugs to parasite- infected cells, especially for the antimalarials in clinical use. Nano-carriers may not only allow the use of potentially toxic antimalarials [15,19,20] but also increase the efficacy of the immune response in vaccine formulations.[16,17,21,22]

The present review intends to highlight the various therapeutic approach used in treating malaria and the advantages of nanotechnology as a promising therapeutic for malaria treatment.

Nanotechnological Strategies for Drug Targeting in Malaria Therapy

The aim of using nano-carriers as drug delivery systems is to promote drug or vaccine protection against extracellular degradation, to improve selectivity in relation to the target, to reduce the frequency of administration and the duration of the treatment and to improve the pharmacokinetic profile of the drug.[10,23,24] For the purposes of this review, the terms "nanosystems" or "nanocarriers" include all the drug carrier systems displaying sizes < 1000 nm. The design of new nanocarriers should consider that, in chemotherapy the plasma maximum concentration (Cmax) of a drug is proportional to its toxic effects and the efficacy is proportional to the area under the curve (AUC) of drug plasma concentration.[25] Nanoparticule drug delivery systems represent a promising approach for obtaining desirable drug like properties by altering the biopharmaceutics and pharmacokinetics property of the drug molecule.[24] In general, long-circulating nanosystems are able to improve the AUC of the drugs and reduce the doses employed in chemotherapy, due to their enhanced selectivity.[26] The most important property of a nanocarrier in the context of malaria is the ability to remain in the blood stream for a long period of time in order to improve the interaction with infected red blood cells (RBCs) and parasite membrane.[26] Additional interesting properties are protection of instable drugs, cell-adhesion properties, and the ability to be surface-modified by conjugation of specific ligands.[24,25] It is noteworthy that, in the treatment of cerebral malaria, most of these potential benefits can be achieved by colloidal nanocarriers that fit intravenous administration. In uncomplicated malaria, the non-parenteral routes are preferred, but they reduce the spectrum of possibilities in terms of the use of drug nanocarriers. Many efforts have been made to implementation of nanotechnologies in the context of malaria treatment.[27,28]

The main strategies for targeting antimalarial drugs to the infected erythrocytes and occasionally, the hepatocytes using nanocarriers by the intravenous route are passive and active targeting. Passive targeting is achieved using conventional nanocarriers (e.g., liposomes, hydrophobic polymeric nanoparticles) [23], or surface-modified long-circulating nanocarriers (e.g., PEGylated).[10,26,27] In contrast, active targeting is attained by means of nanocarriers surface-modified with specific ligands such as carbohydrates, proteins, peptides or antibodies.[23]

Passive drug targeting with conventional nanocarriers

Passive targeting refers to the accumulation of the drug-loaded carrier at a particular body site due to physicochemical or pharmacological factors.[23,28] Nanocarriers are passively targeted, making use of the pathophysiological and anatomic features.[28]

Cells of the mononuclear phagocyte system (MPS) are a simple target due to their phagocytic properties. In contrast, cells that are deprived of phagocytic activity are much more difficult to target. In fact, passive targeting is less exploited in malaria treatment than in leishmaniasis therapy by the intravenous route, because of differences in the type of infected host cells (RBCs and MPS, respectively). RBCs are phagocytically and endocytically inactive. However, it should be emphasized that conventional nanocarriers employed by the parenteral route are rapidly taken up by MPS cells, delivering the drug inside macrophages. Thus, exposure of phagocytes to nanocarrier overload could lead to an initial blockage of the phagocytic uptake that is resolved within 24 to 48 h, followed by a subsequent two-fold rise in the macrophage capacity.[15] This could reduce the rapid action of an antimalarial drug entrapped in a nanocarrier, but may be a very interesting strategy to generate a depot that releases slowly into the blood, thereby altering the pharmacokinetic profile of a short half-life antimalarial drug. On the other hand, the use of conventional nanocarriers for treating P. vivax infections in which hypnozoites are the dormant forms of the parasite in the hepatocytes, located side by side with Kupffer cells, may be an interesting strategy For example, PQ was entrapped in conventional nanocapsules (NC) and nanospheres (NS) for macrophage targeting. These formulations were tested in vitro and in vivo against leishmaniasis, inducing toxicity reduction.[15,29] Unfortunately, experiments in a malaria model with PQ-loaded nanocarriers were not performed and further investigations are required to validate this approach.

Passive drug targeting with hydrophilic surface-modified nanocarries

The surface-modification of nanocarriers with hydrophilic polymers such as polyethyleneglycol (PEG) delays phagocytosis, resulting in a prolonged drug half-life in the blood and allowing the modulation of the biodistribution and the pharmacokinetic profile of the drug.[27,30,31] Mechanisms include reduced protein adsorption and limited opsonisation and complement activation.[30,32]

Passive targeting to MPS can be used in malaria therapy, though long circulating nanocarriers seem to be more suitable for the intravenous delivery due to the increased contact with RBCs. Also, the reduced volume of distribution of the antimalarial can potentially result in less toxic effects to the tissues.[33,34] One worth mentioning example is the halofantrine (Hf)-loaded-nanocapsules (NC); Hf is a very hydrophobic drug used in the treatment of malaria.[35] Two formulations were designed for intravenous administration: (i) conventional polylactic acid-NC without surface modification and (ii) PLA-PEG NC. Despite the different biodistribution profiles of unloaded NC [35], only a slight difference between the pharmacokinetic parameters of Hf encapsulated in both formulations was found when they were evaluated in *P. berghei*-infected mice.[33,34] These unexpected results might

be a consequence of performing the experiments with heavily-parasitized mice as opposed to healthy animals.

The involvement of the liver and spleen in clearing senescent and parasitized RBC in infected mice might saturate the MPS, thus affecting NC pharmacokinetics, reducing the difference between conventional PLA-NC and long-circulating PLA-PEG NC. This example clearly shows that passive targeting was probably achieved in malaria-infected mice even in those with unmodified PLA nanocapsules, because of MPS saturation. On the other hand, these results suggest that infected-mice models should be used to establish the real pharmacokinetic profile of an antimalarial associated with NC, taking into account the influence of the disease on nanocarrier biodistribution.[33,34]

Active drug targeting with surface-modified nanocarriers

Active targeting of therapeutic drugs associated with nanocarriers is achieved by conjugating a cell-specific ligand at the surface of the carrier, thereby allowing a preferential accumulation of the drug in the target cell or tissue [31]. This approach may be successful if the receptors for surface-bound ligands are expressed uniquely in diseased cells or if their expression is differentially higher in diseased cells as compared to normal ones. In the case of malaria, erythrocytes in the blood and hepatocytes in the liver are the main targets. The identification of new Plasmodium or infected cell targets can also be used to modify existing drug delivery systems employing nanotechnology to more efficiently deliver antimalarial drug molecules to the newly-targeted sites of action. However, the disadvantage in this approach is that ligand-attached nanocarriers may induce an undesirable immunological response, due to the proteic nature of some ligands. Another challenge is to adjust the number of ligands per nanocarrier and the suitable PEG chain length at the surface of nanocarriers to properly expose the ligand for cell recognition.[31] Even though this it is a difficult task, the benefits of such a strategy may have an important role in malaria treatment, especially for parenteral administration in the management of cerebral malaria. Thus, the targeting of moieties that are natural candidates for attachment to nanocarriers are peptides, antibodies and, particularly, small carbohydrate-based molecules.

Few attempts using active targeting strategy in experimental malaria treatment with colloidal nanocarriers have been investigated.[36] To date, the active targeting approach was explored using liposomes [34,37] solid lipid nanoparticles (SLN).[37]

Conclusion

Scientific developments and increasing interest in the fight against malaria and other resistant diseases have promoted our ability to work with and understand the nano scale. Nanotechnology is the current leading frontier in research through its aim to manufacture from the 'bottom-up' rather than from the 'top down'. This is because of the vast opportunities it could provide for improving the efficacy and proper targeting of the current anti-malarial drugs used in malaria therapy, as well as possible new drugs characterized by poor solubility, bioavailability and high toxicity profile. In an area such as malaria thereby, nanotechnology has the potential to empower a local response to challenges such as the diagnosis and treatment and prevention of this deadly disease and we can see its' as a better approach to solve out the all problems.

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