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Nanotechnology A Potential Tool In Malarial Chemotherapy-Review

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Abstract
Parasitic diseases are of immense global significance as around 30% of world's population experiences parasitic infections. Amongst various parasitic infections, malaria is the most life threatening disease and accounts for one to two million deaths round the globe every year. Currently no effective vaccine against malaria is available. A major reason for the failure to eradicate malaria has been the shortcomings of malaria preventive and curative drug treatments**.** New effective antimalarial agents are urgently needed due to increasing drug resistance of Plasmodium falciparum. Nanotechnology has the potential to take treatments for diseases to a whole new level. 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 of current anti-malarial 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.

Keywords: Antimalarial agents, Nanomedicine, Plasmodium,

1. Introduction
Malaria is an acute and a chronic infection caused by protozoan of the genus Plasmodium. Clinical manifestations are fever, chills, prostration, and anemia, whereas severe disease can include metabolic acidosis, cerebral malaria, and multi-organ system failure, coma and death may ensue [1, 2]. Four species cause diseases in humans: *P. vivax, P. ovale, P. malariae, and P. falciparum. P. falciparum* the most virulent of the four human malarial parasites, causing the most deadly and severe cases [3]. New class of antimalarial drugs is urgently needed due to increased resistance of *P. falciparum* against most currently used antimalarials [4]. The antimalarial drugs are used for prophylactic suppressive chemotherapy of malaria but various toxicity and resistance problems associated with such chemotherapy need some sustained delivery and safer carriers. Dendrimers are recently reported as carriers for various chemotherapeutic agents [5].
Nanotechnology is a multidisciplinary field covering the design, manipulation, characterisation, production and application of structures, devices and systems at nanometer scale (1-500 nm size range) which at this size range present with unique or superior physicochemical properties. This scale represents that of atoms, molecules and macromolecules [6].The application of nanotechnology in the health care sector, in imaging, diagnostics, drug delivery and therapeutics, also referred to as nanomedicine, has gained ground over the past 5 years. The advantage of using nanotechnology is the possibility of controlling the size of the resulting particles and devices [7, 8].

2. Nanotechnology in diagnosis of malaria
Rapid detection and treatment plays an important role in preventing the spread of malaria. In addition, improper diagnosis and treatment may also result in drug abuse or unexpected side effects [9]. Therefore, simple yet accurate diagnostic devices are required to minimize improper use of anti-malarial drugs or antibiotics. Biomedical nanotechnology offers cutting-edge prospects in the fight against infectious diseases, particularly through the development of more sensitive and specific tools for detection of infectious agents, and other biomarkers. The use of nanotechnology (Fig.1) in molecular diagnostics has been recognized as essential to the development of personalized medicine where some diagnostic procedures are to be performed at the point-of-car [10, 11]. The diagnosis of malaria is often not straightforward. The use of malaria rapid detection tests depends upon production of a reproducible assay with acceptable

high sensitivity and specificity, rapidity, ease of performance and interpretation, stability to storage, species differentiation and all at an affordable price. If these devices reliably equal or surpass the efficacy of clinical microscopy, the accepted 'gold standard' despite its significant limitations, they could have a significant role in clinical practice [12].

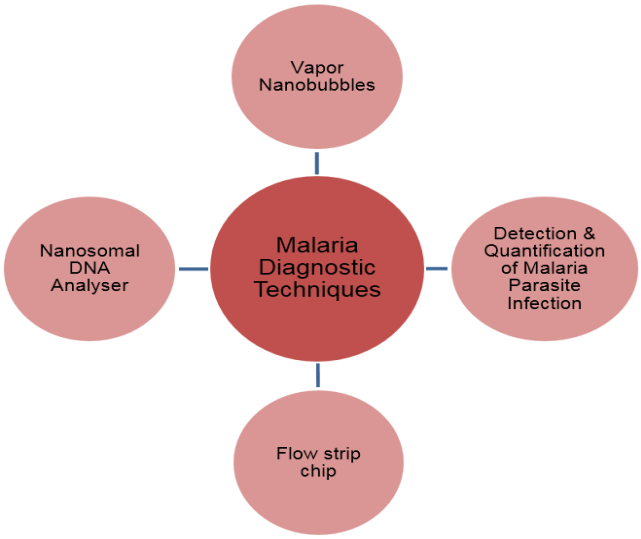

Fig 1:

2.1 Nanosomal smartphone-like malaria detection/ Nanosomal DNA analyser

Cutting-edge nanotechnology is being used to develop an affordable, easy to use startphone-like device able to analyse malaria strain DNA from a finger-prick of blood in 15 minutes. This enables a personalised prescription of drug combinations to be given to patients straight away. The Nanosomal consortium, led by St George's University of London and biotech company QuantuMDx, developed the device in response to WHO warnings of the growth of drug resistance [13].

2.2 Vapor nanobubbles

Malarial therapeutic drugs can be incorporated into nanoscale bubble like structures called as nanobubbles. These nanobubbles remain stable at room temperature and when heated to physiological temperature within the body coalesce to form microbubbles. These bubbles target the tumour tissue and delivering the drug selectively under the influence of ultrasound exposure. This shows the increased intracellular uptake of the drug by tumour cells. It provides an additional advantage of enabling visualisation of the tumour by means of ultrasound methods [14]. Rice University researchers have developed a noninvasive technology that accurately detects low levels of malaria infection through the skin in seconds with a laser scanner. The "vapor nanobubble" technology requires no dyes or diagnostic chemicals, and there is no need to draw blood. The new diagnostic technology uses a low-powered laser that creates tiny vapor "nanobubbles" inside malaria-infected cells. The bursting bubbles have a unique acoustic signature that allows for an extremely sensitive diagnosis [15, 16].

2.3 Detection and quantification of malaria parasite infection.

Microscopy- based imaging and counts of the cells stained with the two methods were used to detect and quantify the infection. (i) Giemsa staining was used as a standard approach to identify ring and schizont stages of malaria parasite development and to measure the level of parasitemia—that is, the ratio of the malaria parasite-infected cells to the total number of cells. (ii) Fluorescent staining with SYBR green I was used as an additional independent method to identify malaria parasite-infected cells and specific stages of the parasite development [17-19] SYBR green I staining was also used to identify viable parasites.

2.4 Flow strip chip for diagnosis of malaria infection

To overcome the need for well-trained experts and equipment, nano/microfluidic technologies can be used to develop devices for fast and accurate malaria diagnosis [20]. Rathod *et al.* developed microfluidic channels to study malaria pathogenesis related complex interactions between host cell ligands and parasitized erythrocytes. Since the microfluidic channels successfully mimic the sizes and shapes of capillary blood vessels, they could observe host–parasite interaction and malaria-infected red blood cells in capillary environment. The malaria diagnostic device is inexpensive and handheld for on-site analysis of patient samples and only requires micro liter sample volume. Therefore, it has the potential to be widely used at field sites for more accurate malaria diagnosis [21].

3 Nanotechnology in treatment of malaria

Malaria is a life-threatening disease and accounts for 1 million to 2 million deaths round the globe every year [22]. Existing treatments for malaria include a limited number of clinically effective anti-malarial agents such as chloroquine, amodiaquine, sulphadoxine and pyrimethamine, etc. However, the clinical utility of most of the antimalarial agents is hampered due to problems such as poor oral bioavailability and the emergence of drug-resistant parasite strains. The coincidental proliferation of resistance to the commonly deployed first-line therapeutics poses a major threat to national and international targets to reduce child mortality due to malaria by one-third by the year 2015 [23]. The main goal of malaria therapy is to promote a high drug concentration in the intracellular parasitophorous vacuoles where the Plasmodium is hosted. Thus the main drawbacks of conventional malaria chemotherapy is the development of multiple drug resistance and the non-specific localization to intracellular parasites, resulting in high dose requirements and subsequent intolerable side effect which eventually leads to patient non compliance [24, 25].

Nanotechnology-based drug delivery systems for malaria have been evaluated since they are able to deliver the drug to the specific target in the human body where the malaria parasite is located. Some of these novel drug delivery systems (NDDS) could be used for both the active and passive targeting of the antimalarials to the site where the parasite is located. Conventional nanocarriers such as liposomes, polymeric nanoparticles, and surface-modified long-circulating nanocarriers like polyethyleneglycol (PEG)-coated particles, could be employed in passive targeting [26, 27]. Nanocarriers are useful tools to improve the pharmacokinetic profile of effective drugs that have limited pharmacotherapeutic application due to high toxicity, low bioavailability and poor water solubility [28-30].

Nanosized carriers have been receiving special attention with the aim of minimizing the side effects of drug therapy, such as poor bioavailability and the selectivity of drugs [31].The aim of using nanocarriers 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 [32]. A number of strategies to deliver antimalarial using nanocarriers and the mechanisms that facilitate their targeting to Plasmodium specific infected cells have been studied. The most important property of a nanocarrier in malaria therapy 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 membranes, protection of unstable drugs, cell-adhesion properties, and the ability to be surface-modified by conjugation of specific ligands [33, 34].

3.1 The potential of nanocarriers as drug delivery systems

[1] Exhibit higher intracellular uptake.
[2] Can penetrate the submucosal layers while the microcarriers are predominantly localized on the epithelial lining.
[3] Can be administered into systemic circulation without the problems of particle aggregation or blockage of fine blood capillaries.
[4] The development of targeted delivery is firmly built on extensive experience in pharmacochemistry, pharmacology, toxicology, and nowadays is being pursued as a multi-and interdisciplinary effort.

Foger *et al*. reported that new effective antimalarial agents are urgently needed due to increasing drug resistance of Plasmodium falciparum. Phosphorothioate antisense oligodeoxynucleotides (ODNs) silencing of malarial topoisomerase II gene has shown to possess promising features as anti malarial agents. In order to improve stability and to increase intracellular penetration, ODNs were complexed with the biodegradable polymer chitosan to form solid nanoparticles. Additionally nanoparticles were found to protect ODNs from nuclease degradation [35].

Borhade *et al*. Clotrimazole was formulated in nanoemulsion based system with the aim of improving its solubility and dissolution, which can further used for its preclinical evaluation. Clotrimazole nanoemulsion was prepared using spontaneous nanoemulsification method. Preformulation studies were preformed to evaluate drug-excipient compatibility, solution state pH stability and pH solubility profile. Dissolution profile of clotrimazole nanoemulsion in various media showed 100% drug release within 15 min irrespective of pH of medium [36].

4. Nanotechnology in vaccination of malaria

With very few adjuvants currently being used in marketed human vaccines, a critical need exists for novel immunopotentiators and delivery vehicles capable of eliciting humoral, cellular and mucosal immunity. Such crucial vaccine components could facilitate the development of novel vaccines for treatment of malaria. Various vaccine adjuvants and delivery vehicles being developed that are approximately nanoscale (1000 nm) in size.

4.1 N-trimethylchitosan as a nanocarrier for malaria vaccine

Nnamani *et al*. reported the synthesis of Water-soluble cationic derivative, N, N, N-trimethylchitosan (TMC) was synthesized from chitosan. Nanoparticles of the TMC were prepared in various media [milliQ water, Na_2CO_3 (pH 10.92), Na_2HPO_4 (PBS, pH 9.01 and alhydrogel®] which were characterized as adjuvants for possible vaccine delivery. The nanoparticles were characterized for particle size, surface charge and morphology using microscopy (Phase contrast microscope and Confocal laser scanning microscope), and Malvern zetasizer Nano-ZS. Time-resolved particle size analysis was performed after one month storage of the TMC nanoparticles at 4 °C.

Joshi *et a.l* explore the potential of nanostructured lipid carriers (NLC) for the intravenous delivery of artemether (ARM), a poorly water-soluble antimalarial agent. The NLC of ARM (Nanoject) was formulated by employing a microemulsion template technique. The NLC were evaluated for particle size, encapsulation efficiency, in vitro drug release and in vitro hemolysis. The antimalarial activity of the Nanoject and conventional ARM injectable formulation was evaluated in Plasmodium berghei infected mice. The nanoject released ARM in a sustained manner. Nanoject offers several advantages over the currently marketed oily intramuscular formulation (Larither®).

4.2 Nanoparticle-detained toxins for safe and effective vaccination

A nanoparticle-based toxin-detainment strategy that safely delivers non-disrupted pore-forming toxins for immune processing. Using erythrocyte membrane-coated nanoparticles and staphylococcal α-haemolysin, we demonstrate effective virulence neutralization via spontaneous particle entrapment. Compared with vaccination with heat-denatured toxin, mice vaccinated with the nanoparticle-detained toxin showed superior protective immunity against toxin-mediated adverse effects. We find that the non-disruptive detoxification approach benefited the immunogenicity and efficacy of toxoid vaccines.

5. Conclusion

Scientific developments and increasing international attention have promoted our ability to work with and understand the nano scale. Nanotechnology provides a new focus for research through its aim to manufacture from the ‘bottom-up’ rather than from the ‘top down’. This is because of the numerous opportunities it could provide for improving the efficacy 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, 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 it’s as a better approach to solve out the all problems.

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