TARGETED ANTIMALARIAL POLYMERIC PRODRUGS

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ABSTRACT

Malaria is the most prevalent parasitic disease worldwide and continues to be one of the greatest health challenges. Conventional malaria pharmacotherapy causes the development of multiple drug resistance and non-specific targeting to intracellular parasites, which leads to high dosage requirements and intolerable toxicity to non-diseased organs and tissues. To date, nanosized drug delivery systems have shown immense potential in pharmacotherapy as the discipline of nanomedicine emerges to address the shortcomings of conventional techniques.

This study entails the development of a pH-responsive polymeric prodrug system, able to self-assemble into nanometric micelles to actively target the *Plasmodium* infected erythrocytes only. The micelle morphology constitutes a polymeric corona and drug at the core, having the two components linked by an acid-labile linkage. The pH of the food vacuole within the parasitic erythrocyte is lower than that of healthy cells, and is exploited to render site-specific drug release. Upon release, the hydrophilic segments are excreted by the body due to molar masses below the renal clearance threshold. The surfaces of the micelles are decorated with targeting ligands specific for malaria-infected erythrocytes to ensure selective uptake. The acid-lability of the linkage is an important consideration in the prodrug system and was duly studied in various phenyl and benzyl derived polyvinylpyrrolidone (PVP) model drug systems containing the \( \beta \)-thiopropionate ester, amide and maleimide linkage. Various vinyl ether and \( N \)-vinylpyrrolidone based copolymer systems were also synthesized to determine the ideal amphiphile to self-assemble by solvophobic forces into drug encapsulating nanocarriers.

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