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Synthesis, characterization and in vitro analysis of polymer-based conjugates containing dihydrofolate reductase inhibitors

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Abstract

Malaria is an acute disease that is caused by the protozoan Plasmodium parasites. Drug resistance is the major problem that is hindering the control of this disease. In order to overcome drug resistance to commonly used antimalarials, nanocarriers which are biocompatible, non-toxic, and are able to deliver drugs to the target site were designed. Polyaspartamide-drug conjugates containing antimalarials that inhibit dihydrofolate reductase were prepared and characterized by nuclear magnetic resonance spectroscopy (NMR), Fourier transform spectroscopy (FTIR), X-ray diffraction (XRD), Thermogravimetric analysis (TGA), Scanning electron microscope (SEM), Energy-dispersive X-ray analysis (EDX), particle size analysis, as well as in vitro antiplasmodial analysis and drug release studies at physiological pH values. NMR and FTIR results confirmed the successful incorporation of the drugs onto the conjugates. SEM images of the conjugates showed predominant spherical and cluster of globular morphologies. In vitro release mechanisms of the drugs from the conjugates were slow and sustained. Conjugates containing 4-aminosalicylic acid and pyrimethamine were found to be the most active against the asexual stage of the parasite with an IC50 value of 332.37 ± 6.46nM. Conjugate containing 4-aminoquinoline derivative, pyrimethamine and primaquine exhibited moderate antimalarial activity with an IC50 value of 4.71 ± 0.70 nM.