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Liposomes of dimeric artesunate phospholipid: a combination of dimerization and self-assembly to combat malaria

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Abstract

Artemisinin and its derivatives are highly effective drugs in the treatment of *P. falciparum* malaria. However, their clinical applications face challenges because of short half-life, poor bioavailability and growing drug resistance. In this article, novel dimeric artesunate phospholipid (Di-ART-GPC) based liposomes were developed by combination of dimerization and self-assembly to address these shortcomings. Firstly, Di-ART-GPC conjugate was synthesized by a facile esterification of artesunate (ART) and glycerophosphorylcholine (GPC) and confirmed by MS, ^{1}H-NMR and ^{13}C-NMR. The conjugate was then assembled to form liposomes without excipient by thin film hydration method. The assembled Di-ART-GPC liposomes have typical multilamellar vesicle structure with bilayer morphology as determined by transmission electron microscopy (TEM) and cryogenic electron microscopy (cryo-EM). Moreover, the liposomes displayed an average hydrodynamic diameter of 190 nm and negative zeta potential at –20.35 mV as determined by Zetasizer. The loading capacity of ART was calculated approximately 77.6 % by weight with this liposomal formulation after a simple calculation. *In vitro* drug release and degradation results showed that the Di-ART-GPC liposomes were stable in neutral physiological conditions but effectively degraded to release parent ART in simulated weakly acidic microenvironment. *In vivo* pharmacokinetics study revealed that Di-ART-GPC liposomes and conjugate have longer retention half-life in bloodstream. Importantly, Di-ART-GPC liposomes (IC_{50} 0.39 nM) and the conjugate (IC_{50} 1.90 nM) demonstrated excellent *in vitro* antiplasmodial activities without causing hemolysis of erythrocytes, which were superior to free ART (IC_{50} 5.17 nM) and conventional ART-loaded liposomes (IC_{50} 3.13 nM). Furthermore, the assembled liposomes resulted in enhanced parasites killing in *P. berghei*-infected mice *in vivo* with delayed recrudescence and improved survivability, compared to free ART administration. Based on these encouraging results, Di-