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IMPROVEMENT OF IN-VIVO DISPOSITION CHARACTERISTICS AND ANTI-TUMOR ACTIVITY OF PEG LIPOSOMAL DOXORUBICIN BY rHSA CONJUGATION ONTO SURFACE OF LIPOSOme

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In a series of our previous studies, we have demonstrated that conjugation of recombinant human serum albumin (rHSA) onto the surface of polyethylene glycol (PEG) liposome prolonged the blood circulation time after intravenous administration in rats. Among various conjugation methods we have applied for rHSA conjugation, the modified-SPDP method provided the rHSA-conjugated PEG (rHSA/PEG) liposome showing the highest AUC. Since AUC is one of the most important driving forces for the better tumor targeting of liposomal drug based on enhanced permeability and retention (EPR) effect, we selected the modified-SPDP method to prepare rHSA/PEG liposome for further investigations. In the present study, we evaluated the in-vivo disposition characteristics and anti-tumor activity of rHSA/PEG liposomal doxorubicin (DOX) in solid tumor-bearing mice. It was shown that rHSA/PEG liposome exhibited longer blood circulation time, lower affinity to reticuloendothelial system (RES) and higher disposition into tumor tissue than PEG liposome. These pharmacokinetic advantages obtained by rHSA conjugation were also observed for liposomal DOX. Correspondingly, rHSA/PEG liposomal DOX exhibited higher anti-tumor activity than PEG liposomal DOX. These results clearly indicate that rHSA conjugation onto the surface of PEG liposome would be a useful approach to increase the effectiveness of PEG liposomal DOX.

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HYDROPHOBIZED POLY(VINYLALCOHOL) AS A NANOPARTICLE DRUG CARRIER FOR AMPHOTERICIN B

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Amphotericin B (AmB) is a broad-spectrum fungicidal antibiotic used primarily in the treatment of life-threatening systemic fungal infections. Since AmB is poorly soluble in water and organic solvents, we have synthesized the amphiphilic poly(vinyl alcohol) (PVA 10kDa) and attempted to solubilize and transport AmB by the encapsulation of PVA nanoparticles. Substituted PVA was prepared by dissolving the starting polymer in N-methylpyrrolidone containing triethylamine at 80°C and subsequently adding cholesterol chlorformate, stearyl chloride, oleoyl chloride or octanoyl chloride. Critical micelle concentration (cmc) of the hydrophobized PVA was determined by using N-phenyl-1-naphthylamine (PNA) as a hydrophobic probe in fluorescence spectroscopy. The polymeric nanoparticles forming and loaded occurring simultaneously in the dialysis process when dimethyl sulfoxide (DMSO) was utilized as the solvent for AmB and the polymer, respectively. The formation of monodisperse nanoparticles by the self-assembly of hydrophobized PVA and their complexation with AmB were studied by size exclusion chromatography and dynamic light scattering (DLS) method. The DLS measurement showed that the drug entrapment into the inner core triggers enlargement of the whole nanoparticle structure (15 - 200 nm). The AmB loading amount in the system was up to 30 w/w%, depending on both the hydrophobic moiety and the feed weight ratio of AmB to the polymer. Importantly, AmB encapsulated in hydrophobized PVA nanoparticle was non-haemolytic at 60 µg/mL, whereas Fungizone (AmB-desoxycholate) caused 50 % haemolysis at the level of 10 µg/mL. The biodistribution of AmB loaded in the hydrophobized PVA nanoparticle and liposomal AmB (AmBisome) were compared after a single injection of drug in mice. Relatively long existence in the blood circulation and negligible hepatic distribution of AmB was demonstrated after intravenous injection of the AmB loaded in the hydrophobized PVA nanoparticle.