Synopsis of Original Research Paper

Formulation development of novel drug-encapsulated nanoparticles using ascorbyl acid derivatives

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Ascorbic acid is widely known as antioxidant agent. Recently, many ascorbic acid derivatives were produced for improvement of the stability. Ascorbyl 2,6 dipalmitate (ASC-DP) is a fatty ester derivative of ascorbic acid. It can't form micelle or liposome structure by itself. However, ASC-DP-distearoylphosphatidylethanolamine-polyethylene glycol 2000 (DSPE-PEG) complex was found to form stable nanoparticles. In this study, we prepared and characterized drug-incorporated ASC-DP/DSPE-PEG nanoparticles. DSPE-PEG was used as one of a solubilizing agent. AmphotericinB (AmB) was used as a model drug. Nanoparticles were prepared by hydration method. ASC-DP/DSPE-PEG nanoparticles were prepared at a molar ratio of 1/1. AmB-loaded nanoparticles were prepared from ASC-DP/DSPE-PEG (1/1 molar ratio) with 10 % mol of AmB. Toxicity of AmB-loaded nanoparticles were examined and compared with that of Fungizone® using ddy mouse. Mice were injected intravenously with a single dose of AmB-loaded samples. Minimum lethal dose (MLD) was defined as the minimum dose that produces death in all mice. Renal and hepatic functions were detected by measuring the serum urea, creatinie, GOT and GPT concentrations. The concentration of AmB in plasma after intravenous administration of each sample was determined by high-pressure liquid chromatography. ASC-DP/DSPE-PEG nanoparticles were obtained with the size of ca. 75-110 nm. ASC-DP nanoparticles were prepared only when PEG-lipid derivatives were used as solubilizing agent. ASC-DP/DSPE-PEG nanoparticles enable to incorporate hydrophobic drugs, such as AmB, nystatin, fluconazole, and clarithromycin. AmB (10 mol%)-loaded nanoparticles were obtained with an average particle size of ca. 170nm and were stable for more than 1 week. MLD of Fungizone was 4.0mg/kg, while that of AmB (10 mol%)-loaded nanoparticles was up to 12 mg/kg. When AmB (10 mol%) nanoparticles or Fungizone was administered to mice at a dose of 2.0 mg/kg, Fungizone showed higher renal and hepatic toxicity than AmB (10 mol%)-loaded nanoparticles. These results indicated that incorporation of AmB in ASC-DP/DSPE-PEG reduced the toxicity of AmB. AmB (10 mol%)-loaded nanoparticles demonstrated higher plasma concentration of AmB than Fungizone when samples were administered to mice at a dose of 1.0 mg/kg. In conclusion, AmB was successfully loaded in ASC-DP/DSPE-PEG nanoparticulate system. Because the nanoparticulate system was applicable for the other hydrophobic drugs, it would become a promising drug carrier system.