ABSTRACT

The aim of the present study was to design a controlled delivery system of Irinotecan using PEGylated liposomes to overcome the limitations of conventional i.v. formulation therapy and to investigate its in vivo performance for sustained delivery and possibility of improved safety. This was achieved by critical evaluation of the developed formulation, selective bioanalytical method, pharmacokinetic and toxicity evaluation. PEGylated liposomes of Irinotecan were prepared by the lipid film hydration method. The loading efficiency of the liposome was found to be greater than 72%. The in vitro release of Irinotecan from PEGylated liposome formulations was in a sustained manner and about 80% of the drug was released in 120 hours. The developed liposome was found to be stable at 4°C for three months. Following intravenous administration to Wistar rats, the liposomal formulation showed effective plasma concentration for 96 hrs compared to 12-16 hrs shown by conventional i.v. formulation. Mean C_max value of liposome formulation was significantly less (354.798±85.330 ng/mL for Irinotecan and 34.266±3.975 for SN-38) than conventional i.v. formulation (1829.616±143.918 ng/mL for Irinotecan and 96.340±10.879 for SN-38). The AUC_0-t of the liposome formulation was 3-4 fold higher compared with i.v. formulation. The increase in AUC and decrease in C_max reflects that the liposome formulation of Irinotecan could reduce the toxic complications and limitations of conventional i.v. formulation. Terminal elimination half life of liposomal Irinotecan is higher than Irinotecan i.v. formulation further supporting the hypothesis that liposomal formulation significantly alters the disposition of Irinotecan. The volumes of distribution for Irinotecan and SN-38 were lower for liposome formulation as compared to conventional i.v. formulation. The clearance rate of Irinotecan and SN-38 in circulation is 4-6 times higher for i.v. formulation as compared to liposomal formulation. These results indicate that required concentration of SN-38 is available in the circulation for a longer period of time. In addition to these observations, differences in pharmacokinetic variables between the formulations are correlated to toxicity findings during toxicokinetic evaluation and organ toxicity study. On the basis of the results obtained, it can be concluded that liposome encapsulation of Irinotecan can be a safer alternative to conventional i.v. formulation and a promising drug delivery system for the treatment of advanced colorectal cancer.