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PREPARATION AND PHARMACOKINETICS OF METHOTREXATE DELIVERY SYSTEM USING LONG-CIRCULATING LIPOSOMES

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Long-circulating liposomes have prompted interests in using them as a drug delivery system. This improvements in delivery has been thought to be the results from sustained action of liposomes in plasma without RES uptake. Although methotrexate (MTX) has been one of the most widely used antineoplastc drug, its use was limited by prompt RES uptake. The purpose of this study was to prepare long-circulating liposomes for MTX using highly water-soluble polymer (PEG-PE). *In vitro*, release of MTX from liposomes in phosphate buffer (pH 7.4), rat liver homogenate, and rat plasma was investigated. The pharmacokinetics and organ distribution of free drug, conventional and long-circulating liposomes were also compared with one another after intravenous administration to rats.

The release of MTX from all of the liposomes increased in the order of PBS, plasma and liver homogenate. But the liposomes containing PEG-PE showed the lower release tendency. The clearance patterns of MTX in blood circulation were compared after i.v. injection of various liposomes to rats. AUC of MTX in egg PC/CH/PEG-PE increased 6 times compared with that in egg PC/CH. AUC of MTX in DPPC liposomes containing PEG-PE increased approximately 4 times as much as that in DPPC liposomes without PEG-PE. In addition, the uptake to liver and spleen remarkably decreased at 15 mins after the administration. The uptake of MTX into the kidney was reduced, suggests that the side effect of MTX on kidney can be estimated to decrease. Liposomes containing DPPC were cleared more slowly in the plasma than those containing egg PC, which may be attributed to the rapid oxidation of unsaturated acyl chain of egg PC.