SYNTHESIS AND EVALUATION OF WATER-SOLUBLE POLY(VINYLALCOHOL)-PACLITAXEL CONJUGATE AS A MACROMOLECULAR PRODRUG
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Paclitaxel (PTX) is an antitumor agent for the treatment of various human cancers. Cremophor EL® and ethanol are used to formulate PTX in commercial injection solutions, because of its poor solubility in water. However, these agents cause severe allergic reaction upon intravenous administration. The aim of this study is to synthesize water-soluble macromolecular prodrugs of PTX for enhancing therapeutic efficacy and reducing side effects. Poly(vinyl alcohol)(PVA), water-soluble synthetic polymer, is one of the most promising macromolecules as a drug carrier which is safe and stable in the body. Partially saponified (89 %) PVA of the molecular weight of 85 KDa was used in this study. The 2'-hydroxyl group of PTX was reacted with succinic anhydride and then carboxylic group of the succinyl spacer was coupled to PVA via ethylene diamine spacer, resulting the water-soluble prodrug of poly(vinyl alcohol)-paclitaxel conjugate (PVA-SPTX). The solubility of PTX was greatly enhanced by the conjugation to PVA. PVA-SPTX was incubated at 37°C in the presence of buffers of pH 5 ~ 9. The release of PTX from the conjugate was accelerated at the neutral to basic conditions. PVA-SPTX inhibited the growth of sarcoma 180 cells subcutaneously inoculated in the mice. It was suggested that the water-solubility of PTX was markedly enhanced by the conjugation to PVA and the conjugate, PVA-SPTX, effectively delivered PTX to the tumor tissue due to the enhanced permeability and retention (EPR) effect.

IMPORTANT ROLE OF BILE ACIDS FOR ABSORPTION IMPROVEMENT BY NOVEL ORAL FORMULATION CONTAINING POLYAMINES
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Development of safe formulation that can improve the intestinal absorption of poorly absorbable drugs is very attractive, because a lot of new drug candidates that are poorly soluble/or poorly absorbable are being generated. We have already found that spermine (SPM), a typical polyamine, was able to improve the intestinal absorption of rebamipide classified into BCS Class IV after oral administration, and the combinatorial use of SPM with sodium taurocholate (STC) synergistically enhanced the intestinal absorption without any serious damages. In the present study, we investigated the effect of endogenous bile acids on the absorption improvement by SPM in bile duct ligated (BDL) rats. Furthermore, the absorption-improving effect of combinatorial use of SPM with STC was examined in beagle dogs under fasted condition. Although the absorption of rebamipide was not improved by SPM alone in BDL rats, the combinatorial use with STC improved the absorption of rebamipide. In the beagle dogs, the oral administration of SPM alone did not enhance the absorption of rebamipide, but the combinatorial use with STC improved the absorption as well as in the BDL rats. These results indicate that bile acids are indispensable for the novel formulation containing SPM to improve the absorption of rebamipide after oral administration. Furthermore, we investigated the mechanisms of absorption-improving effect of combinatorial use of SPM with STC on rat small intestine using a Ussing type chamber.