DIFFERENTIAL TRANSPORTER-MEDIATED INTERACTION OF FRUIT JUICE WITH PRAVASTATIN AND PITAVASTATIN IN RATS
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Purpose Our group reported that OATP/Oatp-mediated transport may contribute to intestinal absorption of pravastatin and pitavastatin. Recently, several investigations have indicated that OATP/Oatp-mediated absorption of drugs is a putative site of drug and grapefruit juice (GFJ) interactions. In the present study, we aimed to investigate the effect of GFJ on transporter-mediated absorption of pravastatin and pitavastatin in rats.

Methods Oatp1a5 and Mdr1a-mediated transport was evaluated with *Xenopus* oocytes and LLCPK1 cells, respectively. *In situ* intestinal closed loop and *in vivo* pharmacokinetic studies were performed to evaluate the drug absorption in rats.

Results and Discussion The plasma concentration of pravastatin after oral administration was significantly decreased by coadministration of GFJ, while that of pitavastatin was significantly increased. Similar results were obtained in *in situ* absorption studies in rats. Uptakes of pravastatin and pitavastatin by Oatp1a5 cRNA-injected oocytes were significantly increased compared with those by water-injected oocytes. Naringin, the main constituent flavonoid in GFJ, inhibited the Oatp1a5-mediated uptakes of pravastatin and pitavastatin. Therefore, a decrease of pravastatin absorption in the presence of GFJ may be due to the inhibition of Oatp-mediated transport by naringin. On the other hand, since naringin was found to inhibit Mdr1a-mediated transport of pitavastatin, it was considered that an apparent increase of pitavastatin absorption was caused through an inhibitory effect of naringin on both Oatp1 and Mdr1.

Conclusions Differential effect of GFJ on intestinal absorption between pravastatin and pitavastatin may be due to the effect of naringin on Oatp and Mdr1-mediated transport of pravastatin and pitavastatin in rats.

IMPROVEMENT OF ORAL ABSORPTION BEHAVIOR OF DIGOXIN BY SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) FORMULATION
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Purpose Poorly water soluble drugs often indicate the large intra- and inter-individual difference in absorption kinetics and low bioavailability caused by poor and/or variable in-vivo dissolution behavior. We have succeeded in improving oral absorption behavior of griseofulvin by preparing self-microemulsifying drug delivery system (SMEDDS) formulation. In this study, we tried to improve the bioavailability of digoxin by preparing its SMEDDS formulation.

Methods In order to prepare the optimal SMEDDS formulation for digoxin, providing spontaneously stable microemulsions after oral dosing, *pseudo-ternary* phase diagram was constructed by titration method. Digoxin was orally administered to rats as powders or SMEDDS formulations.

Results and Discussion Based on the solubility of digoxin, Capryol 90, Cremophor EL and Carbitol were selected as oil, surfactant and co-surfactant, respectively. The *pseudo-ternary* phase diagram indicated that SMEDDS, composed of Capryol 90:Cremophor EL:Carbitol = 4:3:3, provided the stable microemulsions for digoxin. The large inter-individual difference in absorption behavior and low bioavailability of digoxin were observed after oral dosing as powders. On the other hand, the oral administration of SMEDDS formulation significantly improved the bioavailability of digoxin and successfully attenuated the inter-individual difference in the absorption kinetics of digoxin, which would be attributed to the improvement of in-vivo dissolution behavior of digoxin by SMEDDS formulation.

Conclusions SMEDDS formulation is quite useful for digoxin to improve the bioavailability and attenuate the inter-individual difference in in-vivo absorption behavior after oral administration.