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IVIVC FOR ORAL ABSORPTION OF CILOSTAZOL, A BCS CLASS II DRUG, BASED ON GITA (GI-TRANSIT-ABSORPTION) MODEL.
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[Purpose] Absorption kinetics of drugs classified into BCS class II should be rate-limited by the dissolution process, but it is difficult to obtain the in-vitro and in-vivo correlation (IVIVC) based on in-vitro dissolution study. The objective of this study is to predict the serum concentration-time profile of cilostazol, a BCS class II drug, after oral administration as suspensions into rats and to obtain a good IVIVC based on GITA model. [Methods] Hammer milled (HM, mean particle diameter 19.3 µm) or Jet milled (JM, 3.3 µm) cilostazol suspension was orally co-administered with large amount of ketoconazole, a typical CYP3A inhibitor, into fasted Wistar female rats. The first pass effect for cilostazol was almost completely suppressed by the co-administration with ketoconazole. The serum concentration-time profiles were predicted based on GITA model with absorption rate and dissolution rate constants, which were evaluated by in-situ closed loop method in each segment of GI tract and by in-vitro dissolution test for HM and JM suspensions. [Results and Discussion] The serum concentration-time profiles predicted based on GITA model were corresponded with observed data and the pharmacokinetic parameters calculated from the predicted curves were almost equivalent to those from observed data for both HM and JM suspensions. [Conclusions] IVIVC for cilostazol suspensions was established based on GITA model, which is quite useful for predicting oral absorption behavior of drugs.

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PHARMACOKINETIC EVALUATION OF ABSORPTION BEHAVIOR OF P-GLYCOPROTEIN SUBSTRATES BASED ON GI-TRANSIT ABSORPTION (GITA) MODEL
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[Purpose] It is well known that many drugs are affected by efflux transporters including P-glycoprotein (P-gp), which is thought to be one of the reasons for low oral bioavailability of many drugs. Therefore, we tried to analyze the absorption behavior of such drugs for understanding the substantial influence of efflux transporters on bioavailability. [Methods] Quinidine, highly absorbable, and digoxin, poorly absorbable, were selected as model drugs of P-gp substrates. The absorbability was estimated in each segment of GI tract with or without verapamil, a P-gp inhibitor, by a conventional in-situ closed loop method. The pharmacokinetic parameters were estimated by plasma concentration-time profile after intravenous administration. Plasma concentration-time profiles of quinidine and digoxin after oral administration were predicted based on GITA model. [Results and Discussion] The absorption rate constant of quinidine was not significantly decreased by verapamil in each intestinal segment. Based on the results obtained by the in-situ closed loop study, we succeeded in predicting the plasma concentration-time curve of quinidine orally administered as solution into rats. These results suggest that a P-gp substrate with high permeability via passive diffusion such as quinidine would hardly be affected by P-gp-mediated efflux. On the other hand, the absorbability of digoxin was significantly increased by verapamil and it is estimated that oral absorption behavior would also be affected by P-gp based on the prediction by GITA model. [Conclusions] Oral absorption of P-gp substrates were successfully predicted by GITA model and the permeability via passive diffusion would be an important factor for the substantial effect of P-gp on their absorption kinetics.