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PREDICTION OF ORAL BIOAVAILABILITY OF DRUGS BASED ON GASTROINTESTINAL-TRANSIT ABSORPTION (GITA) MODEL.
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[Purpose] GITA model developed in our laboratory is quite useful for analyzing and predicting the oral absorption kinetics in detail. In the present study, we tried to develop a simple system for predicting only a value of oral bioavailability (BA) based on GITA model, where GI transit of drugs after oral dosing is utilized to estimate oral BA.

[Methods] The effective intestinal permeability ($P_{eff}$) was determined by an in-situ single-pass intestinal perfusion method and the absorption rate constant ($ka$) was determined by an in-situ closed loop method. Both absorption studies were performed for five different segments of rat small intestine. The relationship between the two parameters was analyzed to estimate the value of $ka$ from $P_{eff}$. And then the oral BA of model drugs such as ampicillin, antipyrine and cephalaxin was calculated based on GITA model, where a single value of $ka$ deduced from the relationship with $P_{eff}$ was used for describing the input function for the convenient use of GITA model for predicting oral BA.

[Results and Discussion] Logarithms of $ka$ values were significantly correlated with $P_{eff}$ values for model drugs, which allowed us to deduce $ka$ values from $P_{eff}$ values for a given drug in a given segment of small intestine. Utilizing $ka$ values obtained as described above, the oral BA values were estimated and compared with the values calculated based on the observed data. Prediction with $ka$ deduced from $P_{eff}$ in lower segments such as upper or lower ileum provided the BA values that were almost equivalent to those calculated based on the observed data.

[Conclusions] GITA model is quite useful for predicting oral BA of drugs and the absorption of drugs from lower segments of small intestine would be determinant for oral BA of drugs.

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THE EFFECT OF WELLSOLVE, A NOVEL SOLUBILIZING AGENT, ON THE INTESTINAL BARRIER FUNCTION AND INTESTINAL ABSORPTION OF GRISEOFULVIN, A BCS CLASS II DRUG, IN RATS
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[Purpose] In this study, we examined the effect of Wellsolve, a novel solubilizing agent, on the function of intestinal membrane barrier and transporters including P-glycoprotein (P-gp) and PEPT1. [Methods] Effect of Wellsolve on the transport of 5(6)-carboxyfluorescein (CF), rhodamine123 and cephalaxin was examined by an in vitro diffusion chamber while intestinal absorption of CF and griseofulvin was examined by an in situ closed loop method. The toxicity study was performed by measuring the release of protein and LDH. [Results and Discussion] From the in vitro diffusion chamber study, Wellsolve did not show any remarkable effect on the transport of CF. However, 20% (v/v) Wellsolve significantly enhanced the intestinal absorption of CF by the in situ absorption study, suggesting that high concentration of Wellsolve might alter the barrier function in the intestine. The serosal to mucosal (secretory) transport of rhodamine123 was significantly inhibited in the presence of 1.0-2.0 (v/v) Wellsolve, but the mucosal to serosal (absorptive) transport was also reduced in its presence, suggesting that it might not affect the function of P-gp in the intestine. The intestinal transport of cephalaxin was not affected in the presence of Wellsolve, suggesting that it might not change the function of PEPT1 in the intestine. In the toxicity studies, we found that 1-10% (v/v) Wellsolve did not change the release of LDH and protein from the intestinal membranes. Furthermore, intestinal absorption of griseofulvin in the presence of 10% (v/v) Wellsolve significantly increased as compared with the control. [Conclusion] Although high concentration of Wellsolve might alter the intestinal barrier function, this novel solubilizing agent at lower concentrations might be a potent and safe for improving the solubility and absorption of poorly water-soluble drugs including griseofulvin.