Development of Pharmacokinetic Evaluation System for Effective Formulation Design (VII): Novel In Vitro Prediction System for Drug Dissolution and Absorption from OD Tablets Containing Poorly Water-Soluble Drugs in Human
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Purpose
An in vitro dissolution test does not necessarily reflect the in vivo absorption kinetics of drugs due to many factors influencing in vivo oral absorption. This is a major obstacle for formulation design to obtain the pharmaceutical bioequivalence. To solve this problem, we have been developing an in vitro prediction system for drug dissolution/absorption in human gastrointestinal tract to estimate the in vivo performance of drug formulations. We previously indicated that our system was able to predict the in vivo absorption of drugs after oral administration of a conventional tablet. In this study, we tried to apply our system to predict the in vivo oral absorption of BCS class II drugs such as valsartan for orally disintegrating tablet (OD tablet) under the dosing conditions where an OD tablet was taken with water and without water.

Methods
Our in vitro prediction system consists of two connected cells (flow-through type), where “G cell” mimics the stomach and “I cell” does the intestine. G cell and I cell were filled with a simulated gastric fluid (SGF, pH 1.6) and a simulated intestinal fluid (SIF, pH5.5) providing the solubility of a given drug similar to that in Fasted State Simulated Intestinal Fluid (FaSSIF), respectively. SGF was constantly pumped into G cell and the outflow from G cell mixed with SIF was flowed into I cell where pH was controlled time-dependently to reflect pH condition in each intestinal segment (pH5.5, 6.5, 7.5 and 6.5) during the intestinal transit. Then, drug concentrations in the filtered outflow from I cell were determined by HPLC.
In the case of taking a tablet with water, a conventional tablet or OD tablet was placed in G cell in the beginning of dissolution study. On the other hand, to reflect the dosing condition for taking an OD tablet without water, an OD tablet suspended with about 2 mL of water was placed in G cell.
First of all, for a reference formulation, plasma concentration-time profile was calculated with convolution method based on the obtained dissolution profile as an input function. The pharmacokinetic parameters except for absorption rate constant (ka) were obtained from human study for a reference formulation and used as a weight function. A value of ka, providing the plasma concentration profile best fit to observed profile, was obtained by simulation study. Then, based on the dissolution profile for the test formulation, plasma concentration profile for the test formulation was calculated by convolution method utilizing pharmacokinetic parameters obtained above from the reference formulation.
Bioequivalence between the test and reference formulations was evaluated based on AUC and Cmax values calculated from each predicted plasma concentration-time profile.

Results
We fixed the several experimental conditions of our in vitro prediction system to provide the dissolution/absorption rate profile similar to that for the reference formulation (conventional tablet taken with water) obtained from human study. Then, plasma concentration-time profile for the reference formulation was calculated by convolution method as described above. After confirming that the calculated plasma concentration profile was coincided with observed one for the reference formulation, the prediction was performed for the test formulation under the condition as fixed above. In the case of OD tablet taken with water, the in vitro dissolution profile was almost the same with that of the reference formulation. On the other hand, the dissolution for OD tablet taken without water was delayed compared with that for the test formulation taken with water. Plasma concentration profiles calculated based on the in vitro dissolution profiles were in good agreement with observed profiles in both dosing conditions. AUC and Cmax values obtained from predicted plasma profile were also very similar with those from observed ones. The prediction errors of AUC and Cmax (taken with water), were -1.27% and -6.73%, respectively, and those of AUC and Cmax (taken without water) were -0.79% and 0.25%, respectively. These results clearly indicate that it would be possible to evaluate the difference in in vivo performance between test and reference formulations even under the condition where an OD tablet was taken without water by utilizing our prediction system. Furthermore, since the supersaturation and precipitation phenomena were observed in the in vitro dissolution study utilizing our prediction system, it would be possible to evaluate the effect of supersaturation and precipitation after dosing by utilizing our prediction system.

Conclusion
Our in vitro prediction system made it possible to estimate the in vivo performance of a test formulation, particularly an OD tablet, after dosing with and without water, by utilizing the data of the reference formulation, suggesting that our system would be very useful for the pharmaceutical development of OD tablets.