Prediction of Food Effects on the Absorption of BCS Class III Drug Based on Dissolution Testing: The Correlation of In Vitro Dissolution and In Vivo Absorption

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Purpose
The purpose of this study is to simulate the impact of food intake on drug release and absorption in vivo using in vitro dissolution method in fed condition and to establish in vitro/in vivo correlation that could predict the bioavailability of drug instead of using difficult, time-consuming and expensive in vivo bioequivalence studies.

Methods
The dissolution of Entecavir (Baraclude™), model compound of BCS class III, was studied using the basket apparatus and paddle apparatus based on a method described in USP. The dissolution media of fed condition which mixture of buffer solution and dietary component (50:50) was composed of NaCl, NaH₂PO₄ and phosphoric acid with adjusted pH 3.0 in 500 ml, maintained at 37.0±0.5°C. Rotation speed of 50, 75 and 100 rpm was used. These sample were measure by high performance liquid chromatography. The Entecavir-tablet I and II which prepared with different release profile were evaluated dissolution by basket method in fed condition. For in vivo bioavailability test in fed condition, entecavir tablet I and II were orally administrated with meal in the beagle dogs and assayed the blood concentration of entecavir by LC MS/MS.

Results
The previous study, absorption of Baraclude™ was altered with food intake, as evidenced by a decrease in Cₘₐₓ 63%, AUC₀₋₄ of 22% and delay in Tₘₐₓ. It shows that Baraclude™ was dissolved more than 75% under fed condition with paddle method at all of rotation speeds. But it shows 10.4%, 56.2% and 67.4% at rotation speed of 50, 75 and 100 rpm under fed condition with basket method. In the condition with basket method, the dissolution of Entecavir-tablet II was higher than that of Entecavir-tablet I. As a result of in vivo beagle dog test, oral exposal of Entecavir-tablet II was higher than that of Entecavir-tablet I in proportion of in vitro dissolution rate. It shows a linear relationship between logarithmic in vivo blood sampling time and in vitro dissolution time assigned to equal AUCₜₐₜ ratios (AUCₜₐₜ, fed/AUCₜₐₜ, fasting).

Conclusion
Despite its limitations, in vitro dissolution method in fed conditions established by our results might help provide a base for predicting in vivo behavior of BCS class III drug.