In Vitro Dissolution of Fluconazole and Dipyridamole in Newly Developed Gastrointestinal Simulator (GIS) Which May Capture In Vivo Dissolution and Drug-Drug Interaction Caused by Acid-Reducing Agents
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Purpose
Weakly basic drugs such as dipyridamole, ketoconazole, and itraconazole exhibit pH-dependent solubility in physiological pH. Therefore, those drugs may display supersaturation and/or precipitation along the gastrointestinal tract. In addition, the oral bioavailabilities of those drugs would be affected by co-administration of acid-reducing agents, which elevate gastric pH to alter the dissolution profile of those drugs. Here we have assessed the feasibility to predict in vivo dissolution of orally administered weak basic drug products with Gastrointestinal simulator (GIS) and compared with the results of USP Apparatus 2.

Methods
The in vitro dissolution of BCS class I fluconazole, and BCS class II basic dipyridamole, were performed in two different dissolution apparatus, USP Apparatus 2 and GIS, which is composed of gastric, duodenal, and jejunal chambers. The dissolution was performed at pH 2.0 and 6.5 as well as pH 6.0 which mimics elevated gastric pH.

Results
In USP Apparatus 2, fluconazole completely dissolved in any tested pH condition, while dipyridamole dissolved 100% at pH 2.0 and <20% at pH 6.0 and 6.5. In GIS, fluconazole dissolved >80% in both gastric pH 2.0 and 6.0 and neither supersaturation nor precipitation could be observed. On the other hand, dipyridamole completely dissolved in the gastric chamber within 10 min at pH 2.0 and both supersaturation and precipitation were observed. As a result, dissolved dipyridamole reached approximately 40% of dose in the duodenal and jejunal chambers, while dissolved dipyridamole reached only <15% at gastric pH 6.0.

Conclusion
USP Apparatus 2 could capture in vivo dissolution profile of BCS class I and III drugs. However, it is hard to predict in vivo dissolution profile of lowly soluble drugs with USP Apparatus 2. The GIS captured the supersaturation and precipitation of dipyridamole as well as the potential of reduced oral bioavailability by drug-drug interaction. Those data suggest that GIS would be suitable to predict in vivo dissolution for lowly soluble drugs, especially BCS class IIb.