Implementation and Evaluation of an In Vitro Methodology for Forecasting Luminal Concentrations and Precipitation in the Fasted Upper Small Intestine

A. Kourentas, M. Vertzoni, N. Stavrinoudakis, C. Reppas, M. Symillides
National and Kapodistrian University of Athens

Purpose
To implement a recently proposed (Symillides et al. 5th BBBB Int. Conference, 2013) in vitro methodology for drug transfer from stomach into the fasted upper small intestine and evaluate its usefulness in predicting luminal concentrations and potential precipitation of ketoconazole.

Methods
A three-compartment in vitro set-up was used. The experimental conditions were designed by using a drug transfer model equation derived from intraluminal data analysis (Symillides et al. 5th BBBB Int. Conference, 2013). The transfer process was evaluated by using simple aqueous solutions at two dose levels (30mg and 300mg) of ranitidine in gastric compartment. Distilled water was initially placed in the duodenal and the reservoir compartments. Predictability of luminal concentrations and precipitation were assessed by using ketoconazole solutions at two dose levels (100mg and 300mg) in gastric compartment. A medium simulating the luminal environment (FaSSIF) was initially placed in the duodenal compartment. Concentrated FaSSIF solutions were placed in the reservoir compartment so that composition of simulated duodenal contents remains unaltered during the experiment.

Results
Transfer of both ranitidine solutions, was achieved reproducibly in all time points (RSD < 4.18%) and according to theoretically expected data values (Bias<5.66%). Transfer of ketoconazole from the duodenal compartment to waste in presence of precipitated ketoconazole was achieved reproducibly (RSD<12.94% and RSD<3.44% for high and low dose, respectively). Total amount per ml and concentration in the duodenal compartment during the entire ketoconazole emptying from the gastric compartment matched the corresponding average luminal data. In vitro precipitated fractions of ketoconazole in the duodenal compartment adequately reflected average luminal data (Psachoulias et al. Pharm Res. 2012).

Conclusion
The optimized in vitro methodology can be applied reproducibly and can provide biorelevant duodenal concentration and precipitation data. Compared with the Psachoulias et al. Pharm Res. 2012 methodology, it could reduce the laboriousness of the experimentation, especially when solid dosage form are evaluated, since it allows for complete automation.

Acknowledgement
This work was performed within the OrBiTo project which is funded by the Innovative Medicines Initiative Joint Undertaking under Grant Agreement No 115369. The authors would like to thank Biorelevant.com for providing SIF powder original.