Optimization of In Situ Rat Small Intestinal Perfusion Models to Study Drug Absorption and Metabolism
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Purpose
We compared the performance of different small intestinal perfusion models: single pass, re-circulating, and closed loop model, to assess the advantages and disadvantages of each model for in vivo permeability measurement. We further developed the recirculating perfusion model to allow simultaneous perfusion of multiple GI segments to improve assay throughput. We then optimized selected perfusion model with mesenteric vein blood sampling to improve perfusion robustness and data reproducibility. Correlation of measured rat vs human in vivo permeability was presented using the optimized intestinal perfusion model.

Methods
Selected rat small intestine segment was surgically isolated and perfused in situ. Perfusion parameters, such as flow rate, intestine length, etc., were evaluated. Changes in drug concentrations in out-perfusate and mesenteric blood samples were monitored to calculate in vivo effective permeability.

Results
The in situ rat small intestinal perfusion model is a versatile and physiologically relevant tool to study intestinal absorption and metabolism. Using reference molecules, we evaluated the advantages and disadvantages of three different perfusion models, i.e., single pass, closed loop, re-circulating perfusion model. Single pass and closed loop methods are simple to implement, but lack data reproducibility and system robustness. Re-circulating model without perfusate reservoir gave the best data reproducibility and system robustness. We also modify the model allowing simultaneous perfusion of multiple GI segments to improve assay throughput. However, all the models have major limitations to study poorly permeable compounds if only drug disappearance from lumen were monitored. Simultaneous collection of lumen perfusate and mesenteric blood samples allowed both monitoring of “disappearance of drug” (in lumen perfusate samples) and “appearance of drug” (in mesenteric blood samples) during intestinal perfusion. This is especially valuable for low permeability compounds measurement. Using this approach, we have analyzed compounds with high and low in vivo permeability. A correlation of rat vs human in vivo permeability was presented. Such data can be very useful to estimate human absorption.

Conclusion
In summary, presented intestinal perfusion data outlined the advantages and disadvantages of different perfusion model. An optimized perfusion model with mesenteric sampling was recommended to overcome the limitation and challenges of other perfusion models.