In Vitro/In Vivo Correlation of Biphasic Dissolution Methods That Mimic Oral Absorption from Simulated Rat Gastrointestinal Fluids
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Purpose
A low volume biphasic dissolution and partition method was used to simulate the gastrointestinal (GI) fluid and luminal conditions of a fasted state rat in order to compare the partition rate of a development compound to in vivo absorption.

Methods
The Biphasic Dissolution assay on the Sirius inForm was divided into 2 sectors representing gastric and intestinal conditions. The immiscible organic layer was added in the intestinal sector as it was understood that minimal absorption took place from the stomach. The recipe for the simulated GI fluids and experiment parameters that represented the rat physiology were defined from a review compiled Bath University.

The development compound was supplied by Pfizer along with formulation and pharmacokinetic data. The samples were prepared as suspensions as used in a preclinical toxicokinetic study.

The in vitro data presented here is the dissolved concentration of compound that partitioned into the organic solvent layer. IVIVC were developed between the in vitro dissolution and the in vivo absorption. In vivo absorption was calculated with numerical deconvolution using PCDCON software.

Results
The aqueous media that contained the simulated rat GI fluids and the suspended sample were too turbid to reliably quantitate dissolved compound using in situ UV absorbance. However, the organic solvent layer remained clear throughout the experiment, which enabled in situ UV quantitation.

The aqueous-organic interface also maintained a barrier to any suspended particles as demonstrated by the near identical partition profiles of the 300 and 1000 mg/Kg dose experiments in Figure 1.

Good linearity between the in vitro and in vivo data was observed (Figure 2) when plotted as the amount partitioned and the percent partitioned in vitro versus the amount and percent absorbed in vivo. However, there was a gender difference in the in vivo data where female rats were found to have a higher level of absorption than the male rats.

Conclusion
This work demonstrated that under biorelevant conditions biphasic dissolution and partition experiments can be used to correlate to in vivo pharmacokinetic data. Future work will be directed towards studying a wider range of compounds using biphasic dissolution and partition methods to develop IVIVC.