Why two organs are better than one:

A gut-liver microphysiological system that mimics human oral and intravenous dosing regimens for improved prediction of oral bioavailability

Abstract

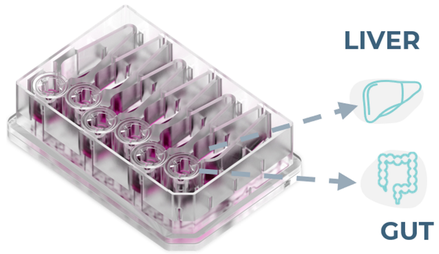
The challenge to continuously improve the *in vitro* to *in vivo* translation of drug efficacy and safety data has driven the emergence of more complex multi-organ microphysiological systems (MPS) that are fluidically linked (Edington et al., 2018). Here, we introduce the PhysioMimix™ Multi-organ plate, (MPS-TL6) with six wells, each containing two compartments - Transwell® and liver. Liquid flow can be independently controlled in each compartment and in the interconnecting channel from the liver to Transwell® to mimic inter and intra-organ blood flow in vivo." at the end of the paragraph/sentence.

In this study, a gut-liver model is described which can be operated as gut only model (mix of Caco-2 and HT-29 cells) to study intestinal permeability or as liver only model (primary human hepatocytes), for the assessment of hepatic first pass metabolism. When combined, crosstalk between the organs can be studied and quantitative assessment of key ADME parameters can be made. Here, the MPS-TL6 is used to estimate oral bioavailability by simulating an oral and IV dose administration in a single plate.

The gut-liver MPS

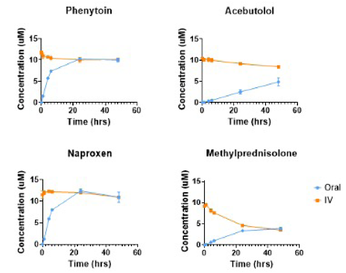
Can be used to determine:

- Intestinal permeability (gut only)
- First pass metabolism (liver only)
- Oral bioavailability (gut & liver)



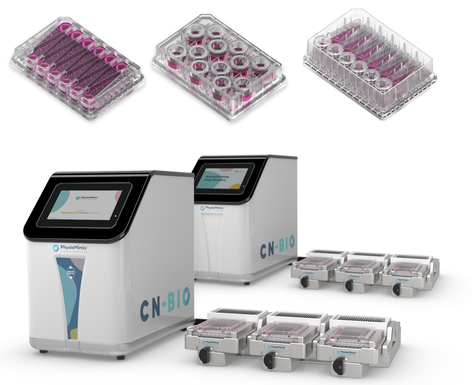
Oral and IV drug concentration profiles

Oral and **IV** dose administration can be performed in a single MPS-TL6 plate.



The PhysioMimix™ Organ-on-a-chip range

- Single or Multi-organ System availability
- Fluidic flow delivers biomechanical stimulus, oxygen and nutrients
- Tuneable flow rates enhance human relevance
- Culture viability is maintained over many weeks
- Gain deep insights from multiple & clinically relevant end points
- Simultaneously run up to 6 plates for increased throughput
- Familiar open-well architecture for ease of use

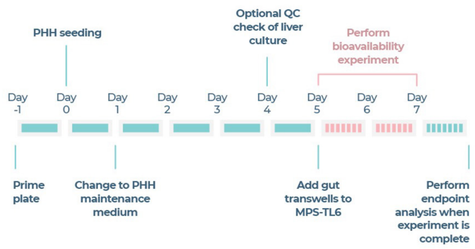


Why gut-liver MPS for oral bioavailability?

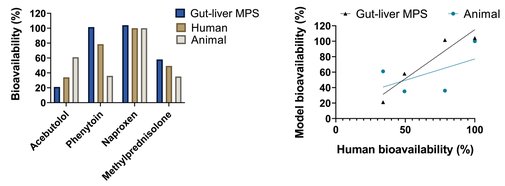
- Animals dominate bioavailability predictions, but correlation is poor: R2 =0.34 from 184 compounds (Musther et al., 2014)
- With the gut-liver MPS, an oral (drug added apically in the gut Transwell) and IV (drug added in plate's media circulation) dose can be performed in a single plate
- Bioavailability can be estimated in less than 10 days

Experiment timeline

4 drugs selected from study by Musther et al., 2014 with known animal bioavailability.



Improved bioavailability predictions vs animals in less than 10 days



Conclusion

- Our human relevant gut-liver MPS can be used to study the gut permeability and liver first pass metabolism of drugs
- Oral and IV dosing regimes can be simulated in a single plate
- The results of this study demonstrate improved bioavailability predictions using the gut-liver MPS compared to animal models

Poster ID 35

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References

Edington CD et al. Sci Rep. 2018;8(1):4530

Musther H et al. Eur. J. Pharm. Sci. 2014; (57):280

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