In Vivo Predictive Dissolution (iPD) to Advance Oral Drug Product Development

Bart Hens, Gordon L. Amidon

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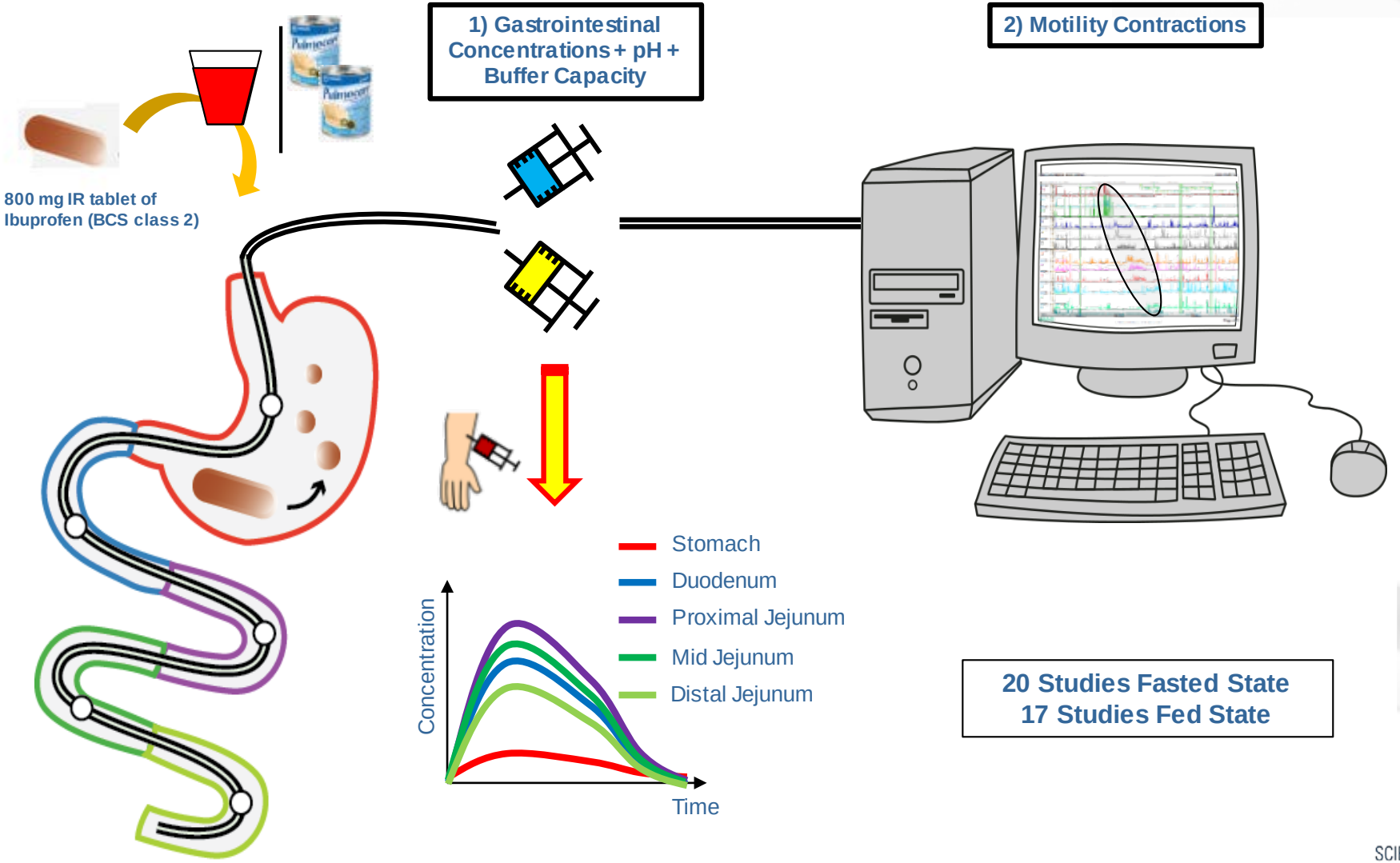
February 22, 2018
'Biorelevant?' Symposium
Copenhagen, Denmark

Disclosure

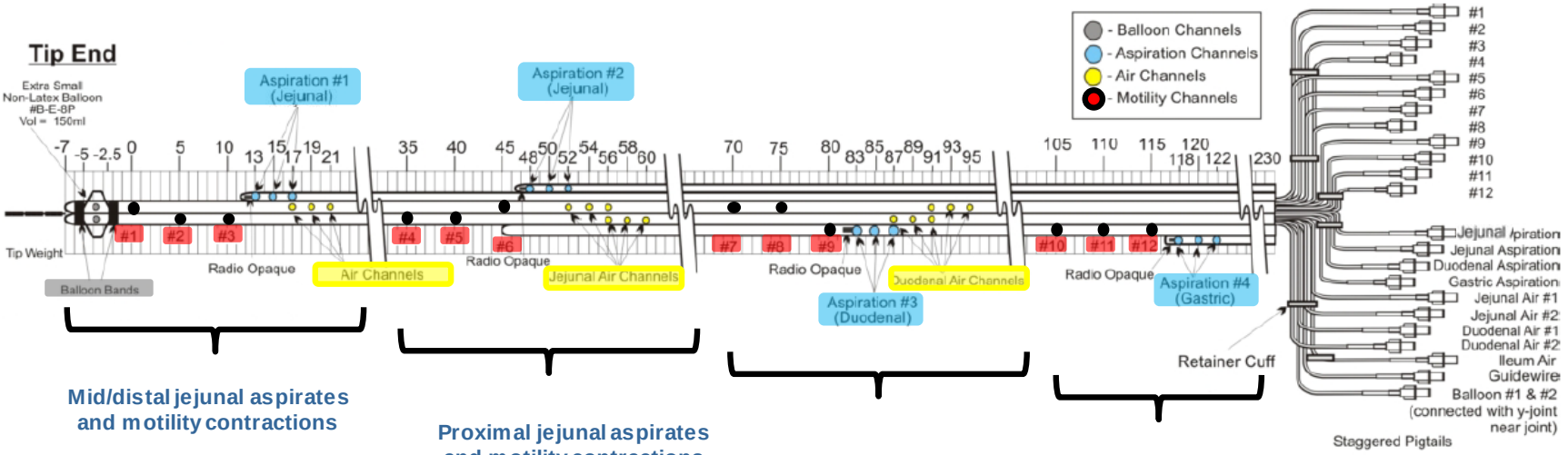
- **Ibuprofen aspiration/motility study**
  - Study Design & Results

- **Optimization of the Gastrointestinal Simulator (GIS)** with an extra focus on:
  - Hydrodynamics
  - Volumes
  - Gastric emptying
  - Absorptive sink
  - Buffer

How to gain insights in human physiology in order to build/optimize this model?



Customized Multi-Channel Aspiration & Motility Catheter

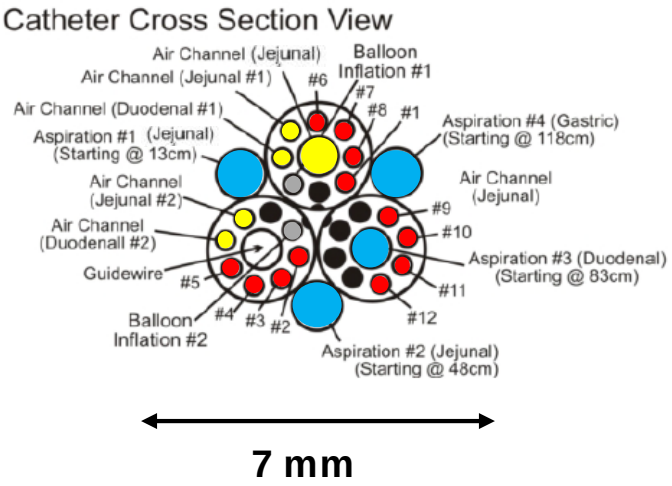


Mid/distal jejunal aspirates and motility contractions

Proximal jejunal aspirates and motility contractions

Duodenal aspirates and motility contractions

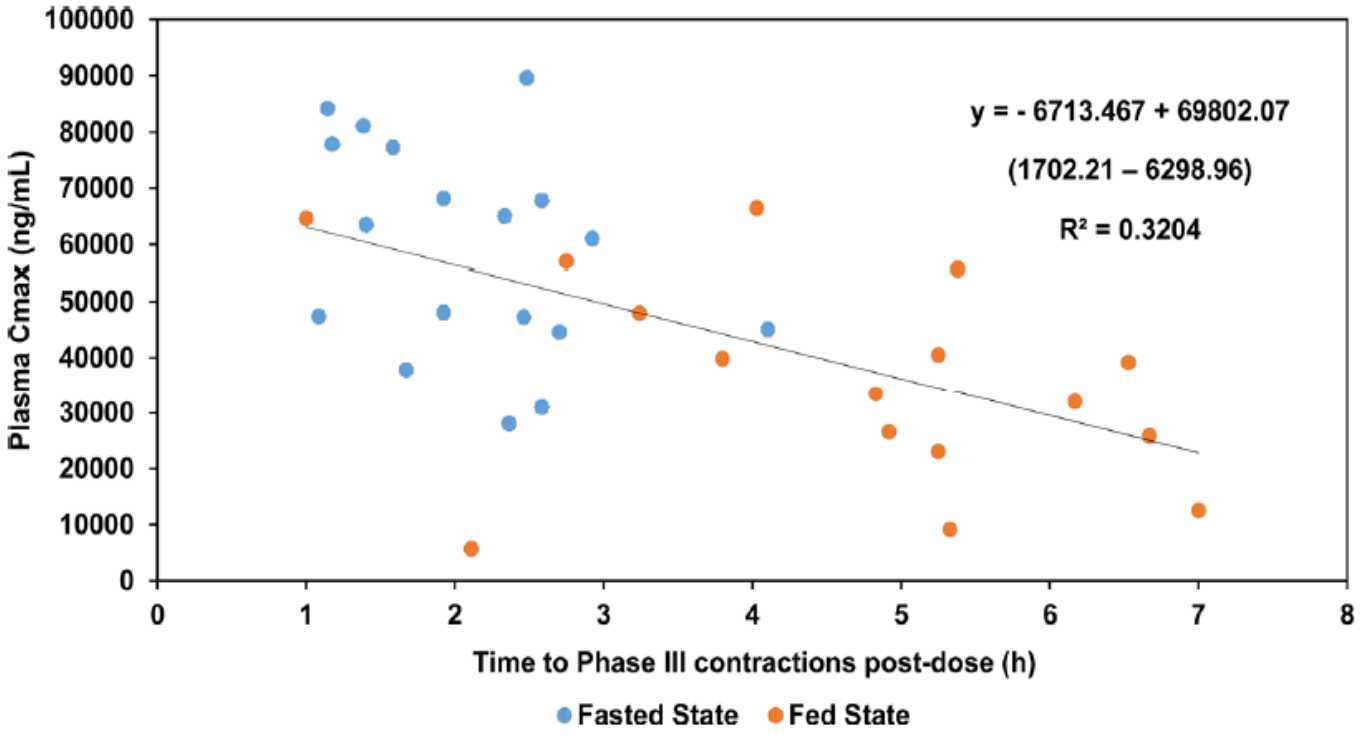
Gastric aspirates and motility contractions



1 cm apart for motility channels (newest design)

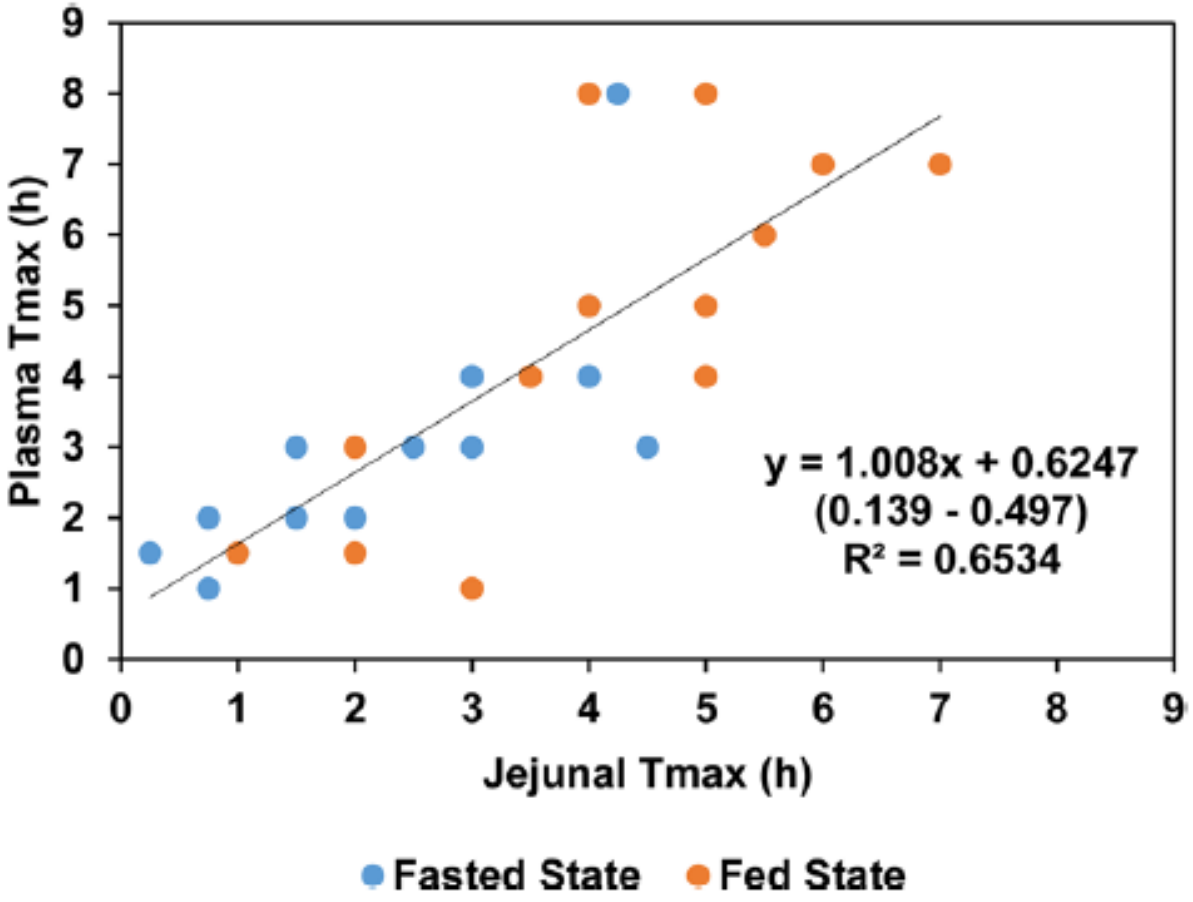
Hens et al. 2017 - doi: 10.1021/acs.molpharmaceut.7b00426.

Plasma C_{max}



Hens et al. 2017 - doi: 10.1021/acs.molpharmaceut.7b00426.

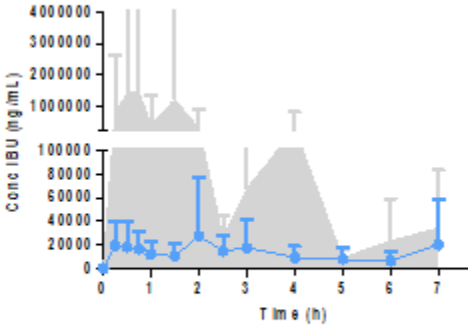
Plasma T_{max}



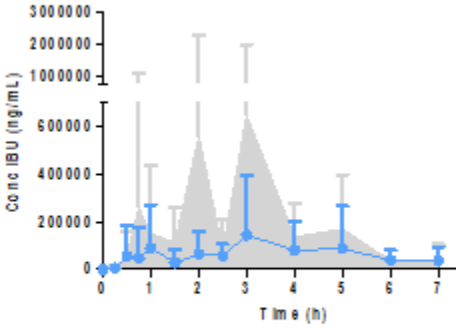
Hens et al. 2017 - doi: 10.1021/acs.molpharmaceut.7b00426.

IBU concentrations in the GI tract: Depending on the dynamic change in pH

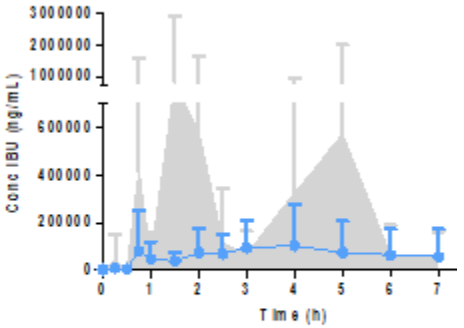
Fasted Stomach



Fasted Duodenum



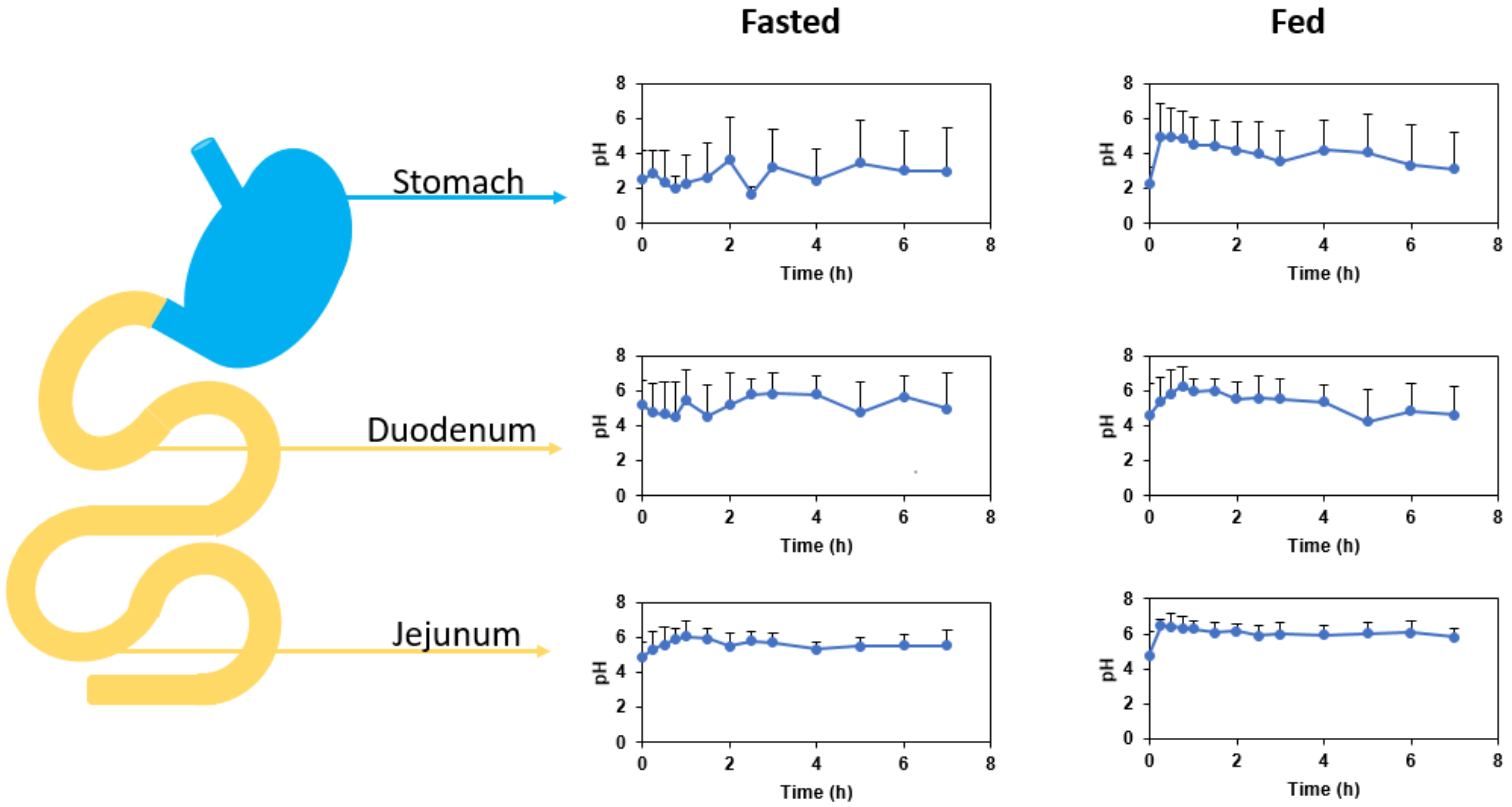
Fasted Jejunum



— Solution Concentrations — Total Concentrations

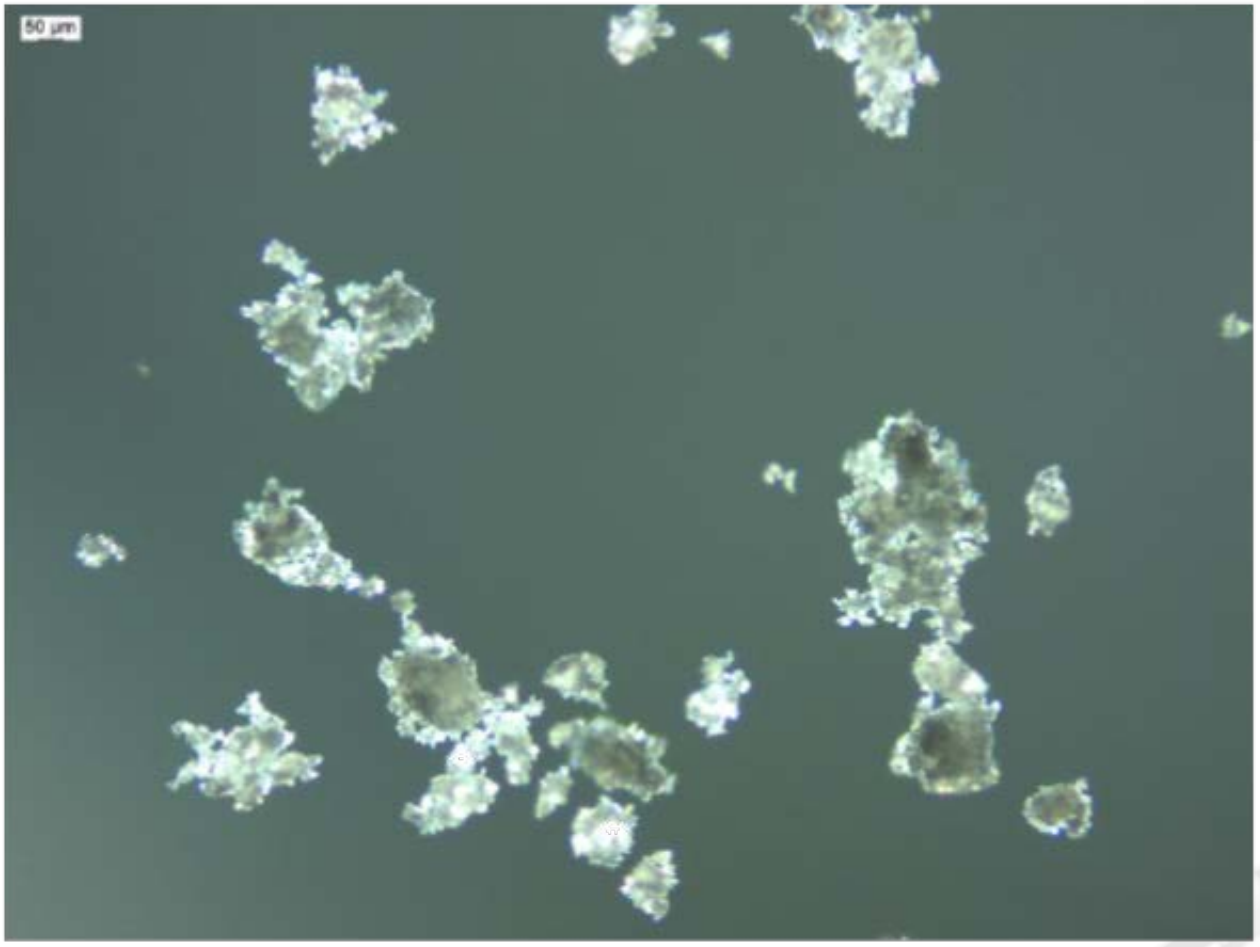
Hens et al. 2017 - doi: 10.1021/acs.molpharmaceut.7b00426.

Dynamic change in pH along the GI tract



Hens et al. 2017 - doi: 10.1021/acs.molpharmaceut.7b00426.

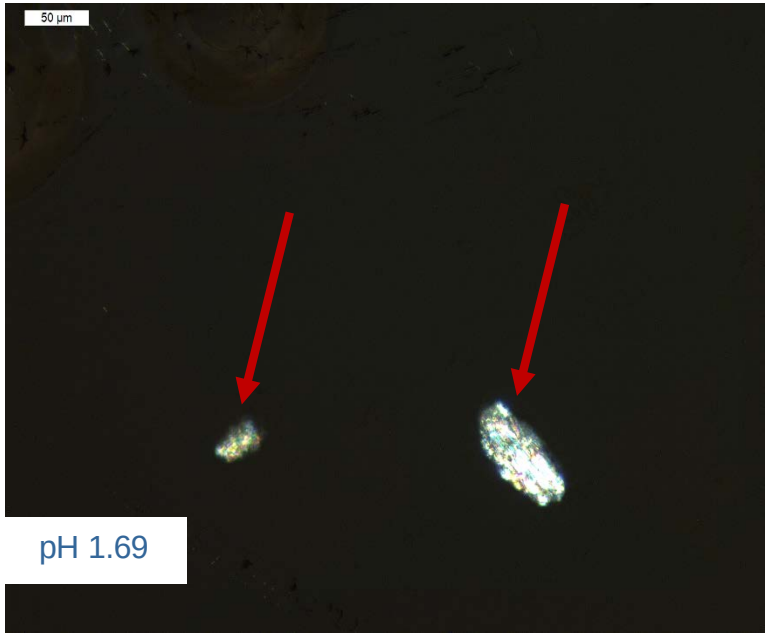
Polarized Optical Microscopy (POM)



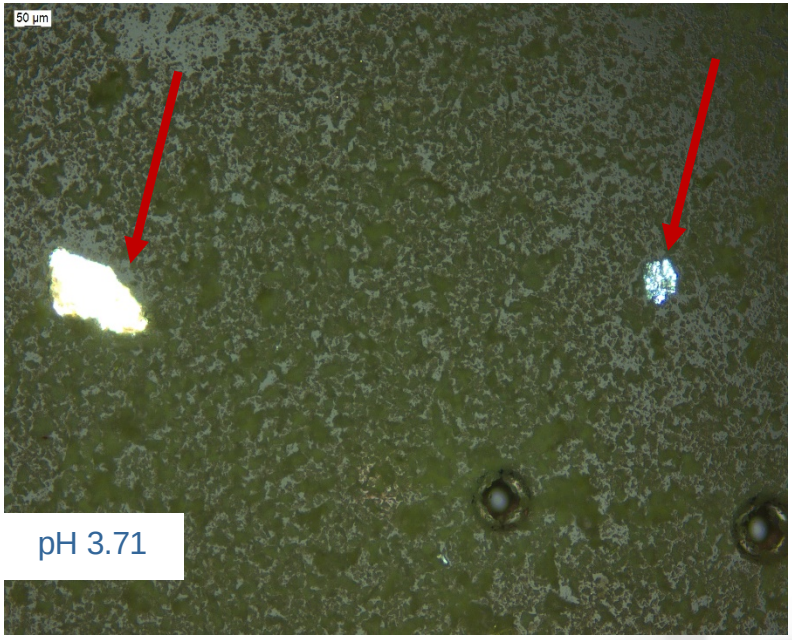
Using polarized light to see the shining of crystal structure of ibuprofen

Microscopy studies with polarized light

Subject 5 – Fasted State



360 min Stomach



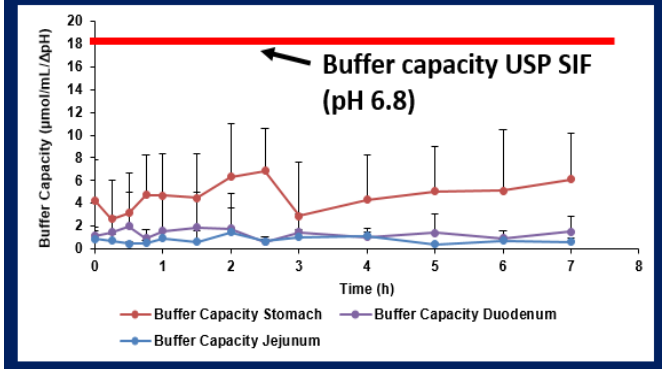
300 min Duodenum

In collaboration with Dr. Naír Rodríguez-Hornedo (University of Michigan)

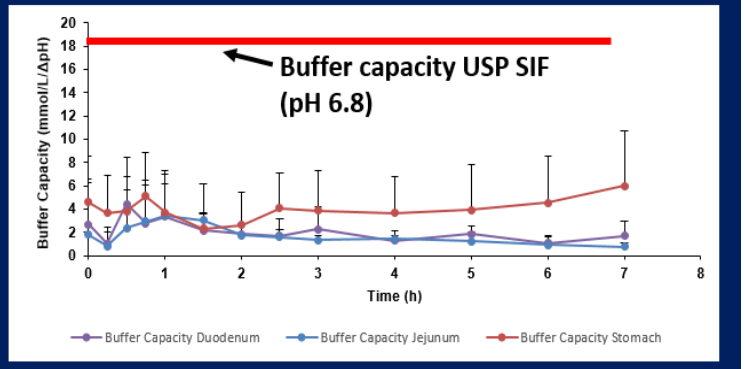
Reason for dynamic pH? Low Buffer Capacity!

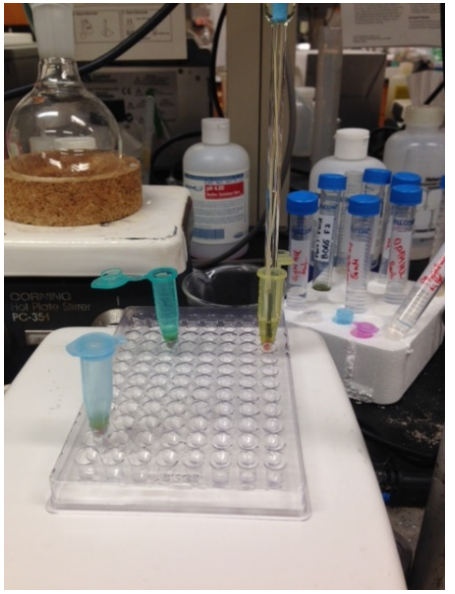
Low Buffer Capacity

Fasted State



Fed State





Buffer Capacity	USP SIF	FaSSIF	FaSSIF-V2	FaHIF
µmol/mL/ΔpH	18.4	12	10	2.4-5.6*

*Fadda et al. 2010. Mol. Pharm.
*Persson et al. 2005. Pharm. Res.

Accepted Manuscript in Mol. Pharm. – Special Issue of OrBiTo

molecular pharmaceutics

Article

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Low Buffer Capacity and Alternating Motility along the Human Gastrointestinal Tract: Implications for *in Vivo* Dissolution and Absorption of Ionizable Drugs

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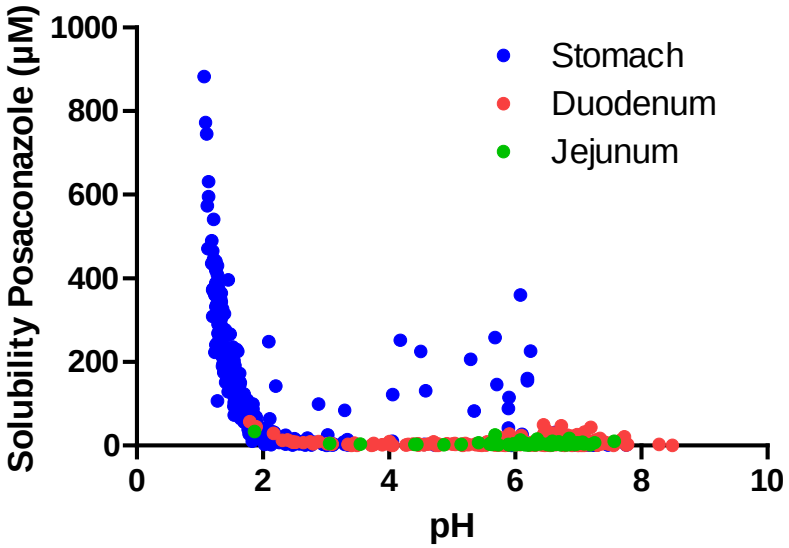
Collected Data During Bart's PhD About Posaconazole – Leuven, Belgium

KU LEUVEN

Fasted

n=597



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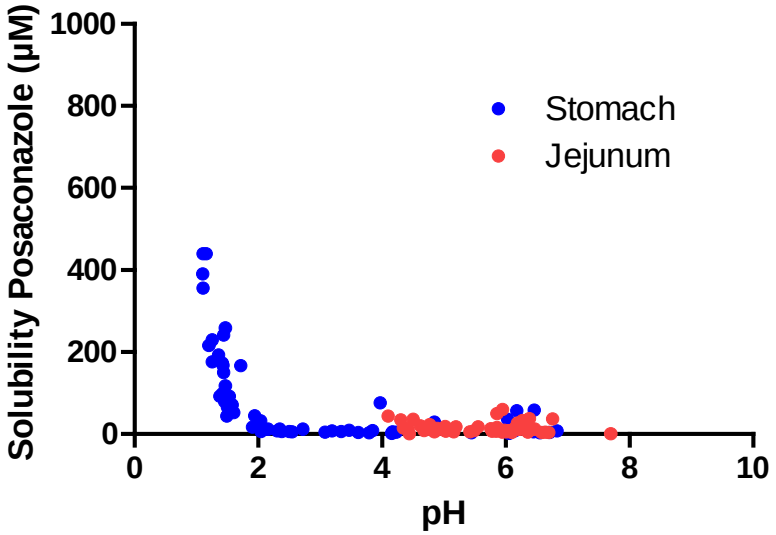
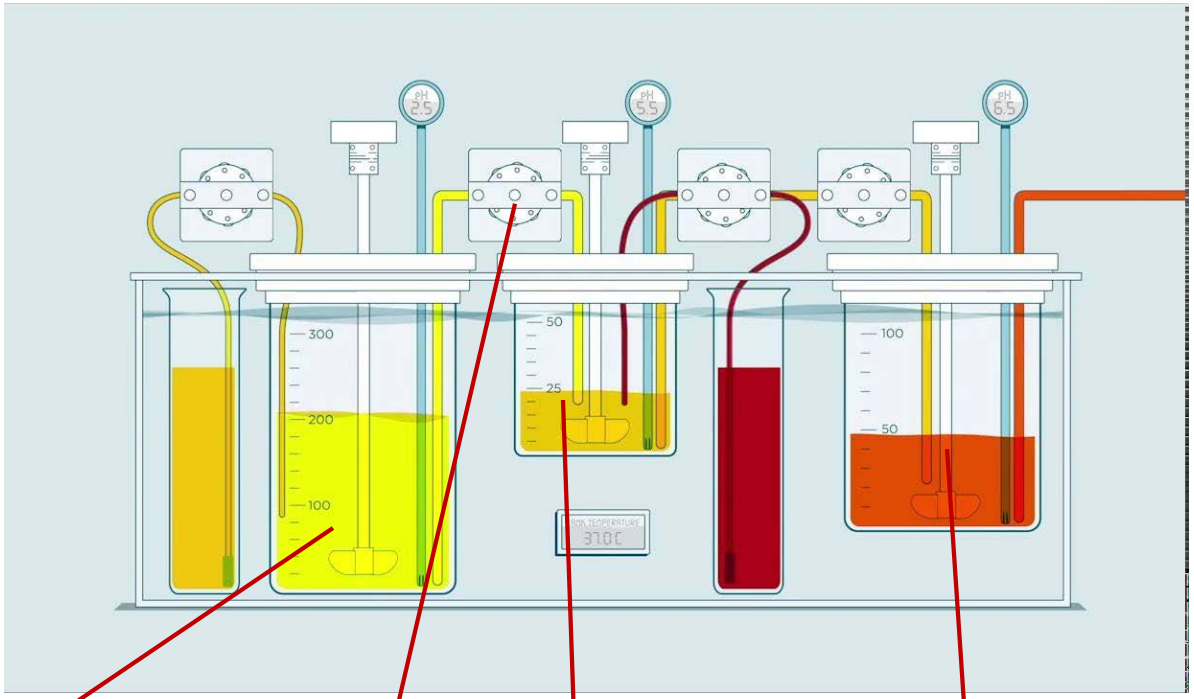
n=118



Hens et al. 2016 - doi: 10.1002/jps.24690. & doi: 10.1016/j.xphs.2016.03.027.

From GIS-1 to GIS-2



- **Vessel design**
- **Hydrodynamics**
- **Mixing**

➔ **Shear rates?**

- Volumes and Transit Times
- Buffer
- Absorptive sink

GIS-1 hydrodynamics

Stomach compartment

- $D_{impeller} \sim 19.47\ mm$
- $D_{tank} = 59\ mm$
- $D_{shaft} = 6.5\ mm$
- $Tank\ curveature = 4\ mm$
- $Distance\ from\ the\ bottom\ of\ the\ tank = 4\ mm$
- $H_{tank} = 108\ mm$
- $Rotational\ speed = 100\ rpm$
- $Re = 907.53 \sim turbulent\ flow$

Volume average shear rate =15.843 1/s

Duodenum compartment

- $D_{impeller} = 30\ mm$
- $D_{tank} = 50.5\ mm$
- $D_{shaft} = 6.5\ mm$
- $Tank\ curveature = 4\ mm$
- $Distance\ from\ the\ bottom\ of\ the\ tank = 4\ mm$
- $H_{tank} = 24.5\ mm$
- $Rotational\ speed = 100\ rpm$
- $Re = 2154.6 \rightarrow turbulent\ flow$

Volume average shear rate =40.19 1/s

Shear rate is the rate at which a progressive shearing deformation is applied to some material.

➔ **Target: Shear rates *in vivo*: 2-4 s^{-1}**

Jim Brasseur et al.

GIS-2 Vessel hydrodynamic modeling

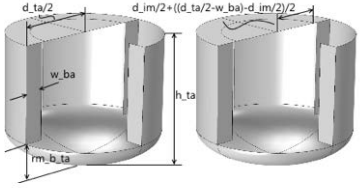
- Simulations of hydrodynamic by computational fluid dynamics (CFD) method, using COMSOL Multiphysics®
- Design considerations are
  - **Stirrer design** (anchor, USP paddle, hydrofoil)


Anchor-Radial

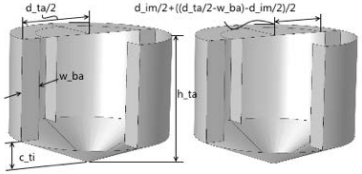

USP paddle


Hydrofoil-Axial

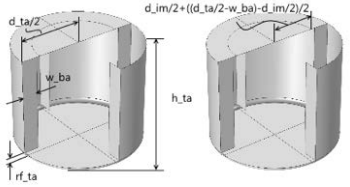
  - **Vessel shape and size** (currently focusing on 75mL and 300 mL)



Dished bottom



Cone bottom

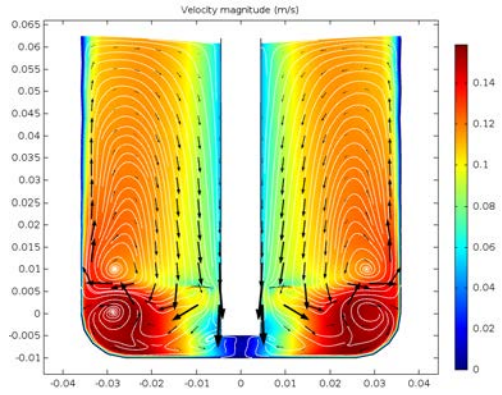


Flat bottom

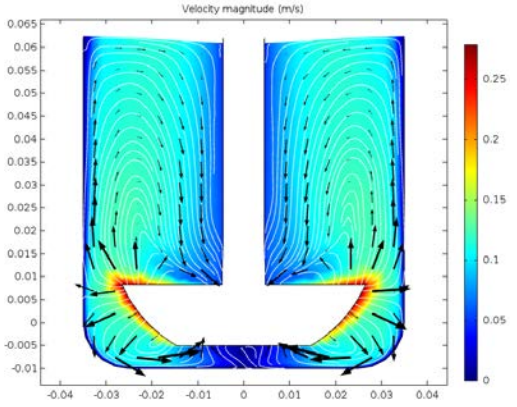
Niloufar Salehi et al.

Design and **3D printing of GIS-2 Vessels**

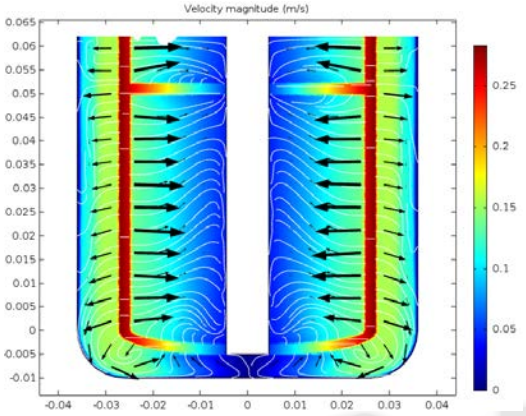
Fluid patterns + Shear rates



Hydrofoil



Paddle

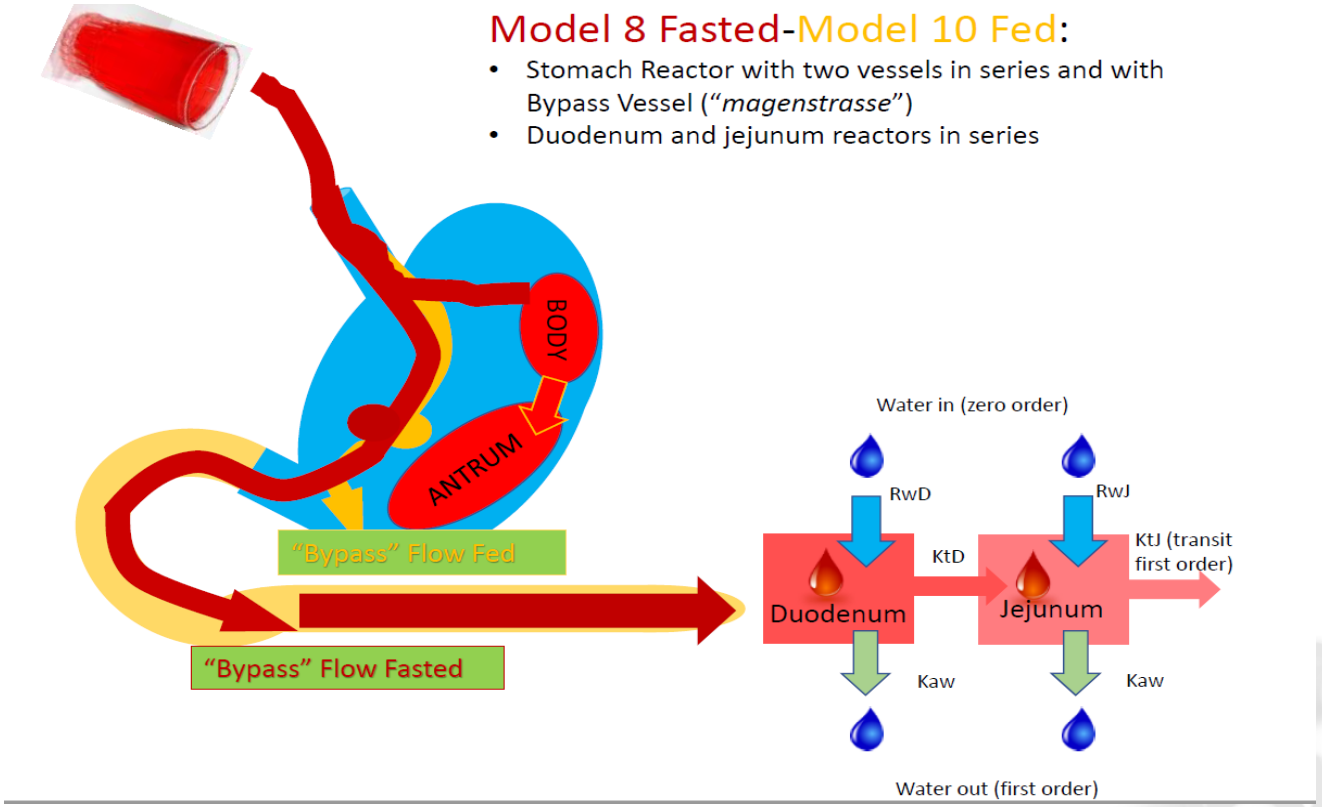


Anchor

Niloufar Salehi et al.

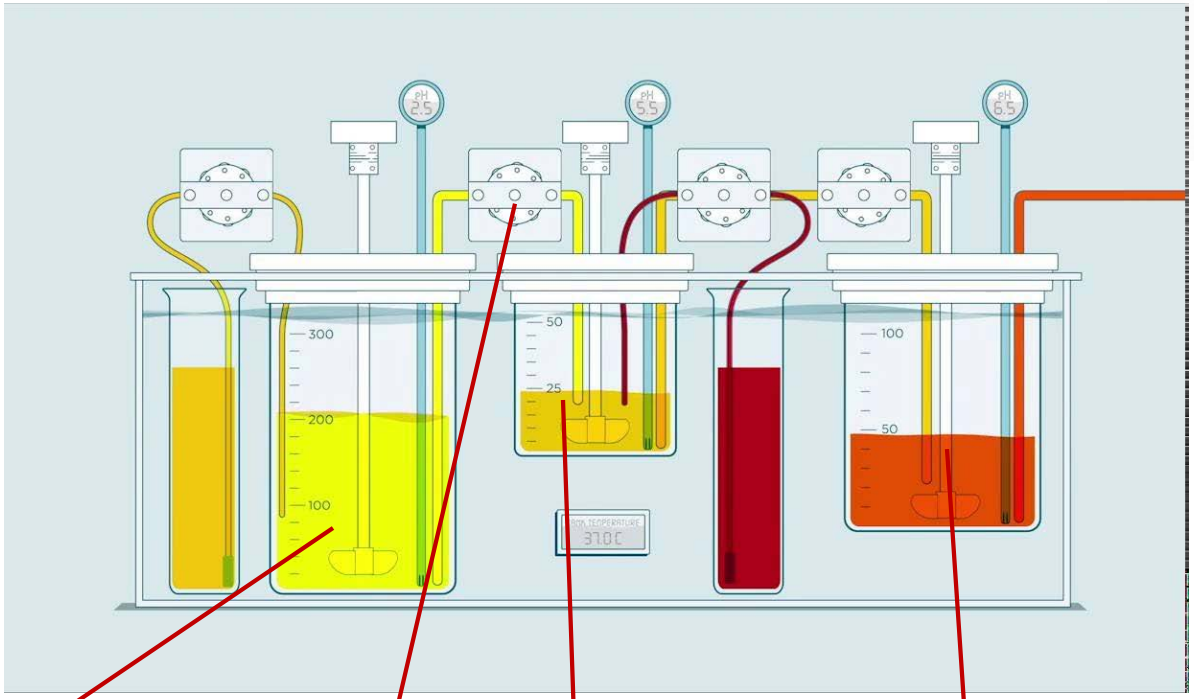
New insights concerning the stomach

Based on collected data we **change from <u>a one-compartmental design of the stomach to a more appropriate, multi-compartmental approach</u>** that **reflects drug distribution along different regions of the stomach**



Paixão/Bermejo et al.

From GIS-1 to GIS-2



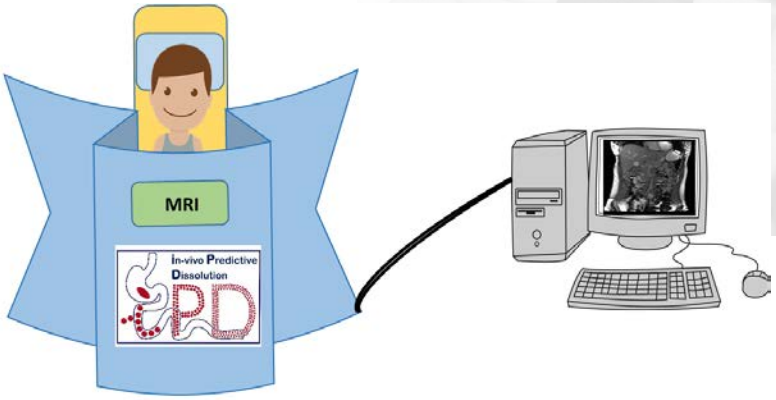
- Vessel design
- Hydrodynamics

➔ Shear rates?

- **Volumes and Transit Times**
- Buffer
- Absorptive sink

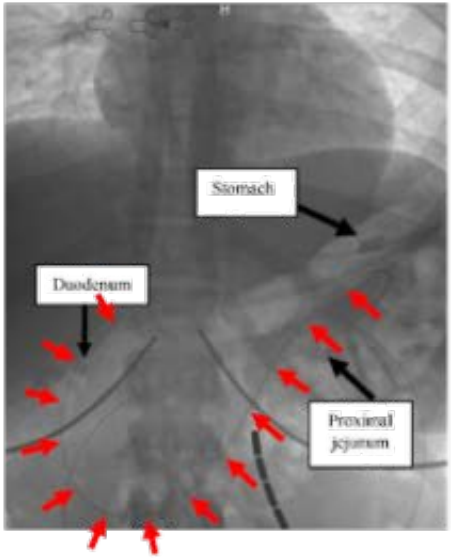
MRI for gastric emptying, bowel water volumes and motility

The University of Nottingham
UNITED KINGDOM

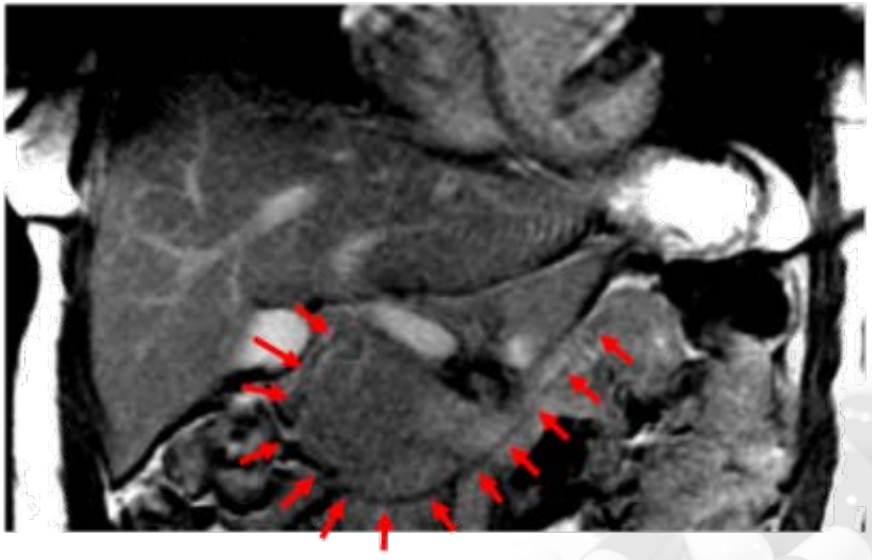


Task 1.3.3 – MRI-manometry study

Michigan – Fluoroscopy
Subject B022_v2



Nottingham –MRI
Subject FDA003_v2



Hens et al, Mol Pharmaceutics 2017

 Luca Marciani et al.

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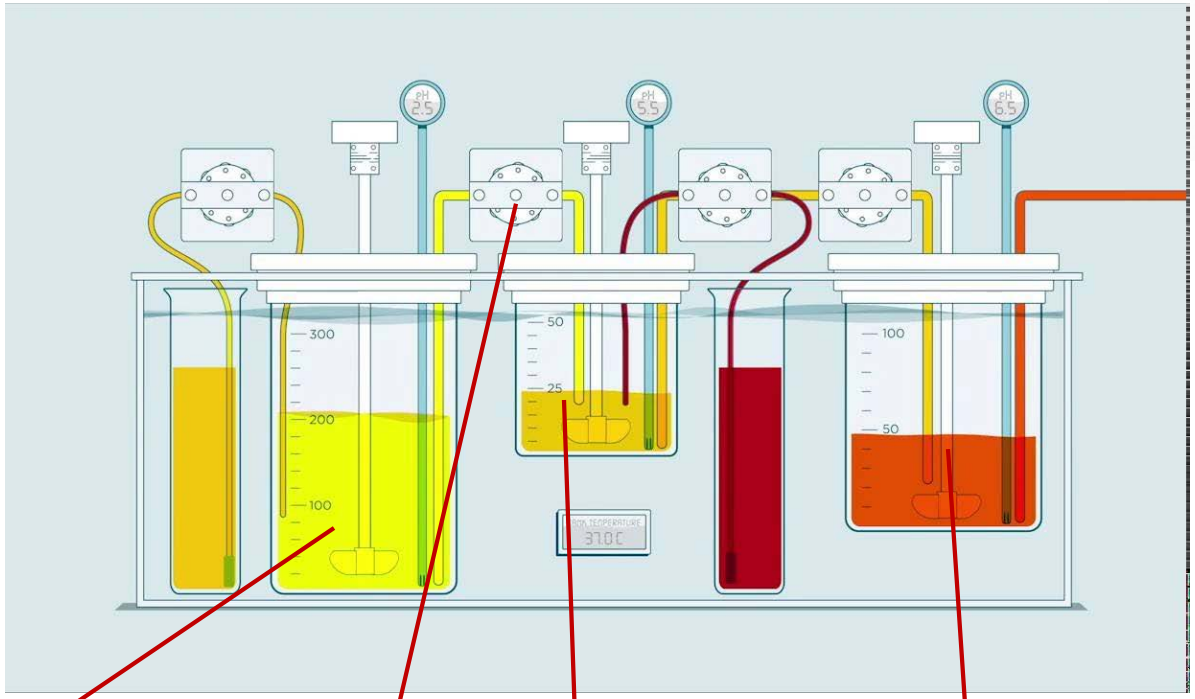
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

From GIS-1 to GIS-2



- Vessel design
- Hydrodynamics

➔ Shear rates?

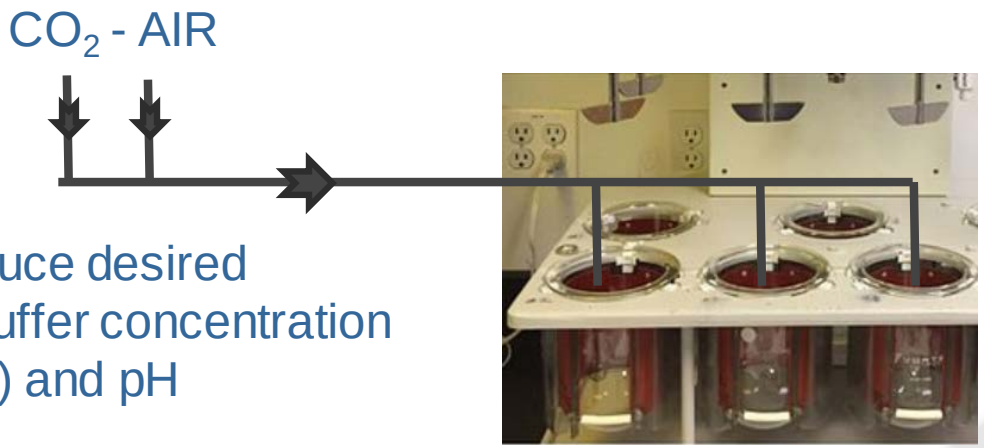
- Volumes and Transit Times

- **Buffer**

- Absorptive sink

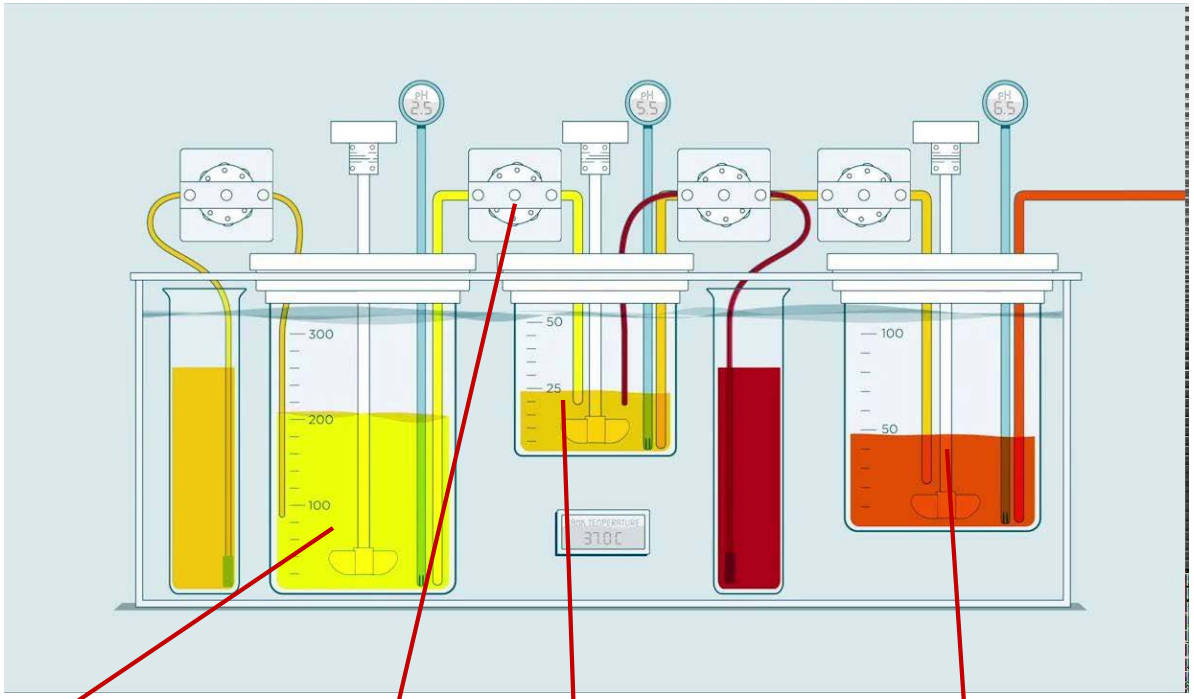
Implementation of multi-vessel bicarbonate buffer dissolution

- USP Apparatus (6 station) dissolution apparatus has been established with bicarbonate buffer in 3 vessels
- Prepared to test RLD and other products
- Next step: implementation in GIS-2



Jozef Al-Gousous et al.

From GIS-1 to GIS-2



- Vessel design
- Hydrodynamics

➔ Shear rates?

- Volumes and Transit Times

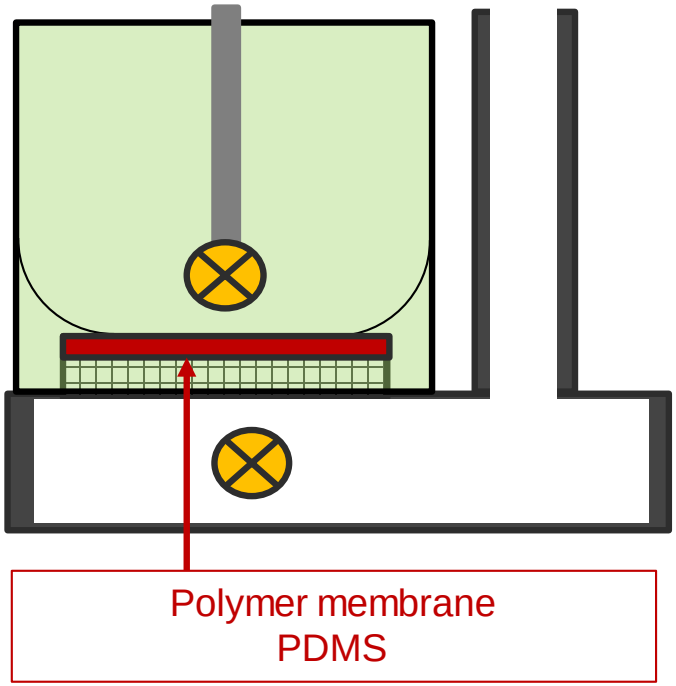
- Buffer

- **Absorptive sink**

Development of polymer membrane to simulate absorption compartment: Poly(dimethylsiloxane) (PDMS)

Absorption chamber design

- **3D printed chambers** have been prepared
- **In-depth *In vitro* characterization of the membrane has been performed**
- **Patented**
- Next step: Implementation in **GIS-2**



molecular pharmaceutics

Article

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In Vitro Characterization of the Biomimetic Properties of Poly(dimethylsiloxane) To Simulate Oral Drug Absorption

Patrick D. Sinko,*[†] David Gidley,[‡] Richard Vallery,[∥] Aaron Lamoureux,[§] Gordon L. Amidon,[†] and Gregory E. Amidon[†]

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[∥]Department of Physics, Grand Valley State University, Allendale, Michigan 49401, United States

Supporting Information

- "**Biomimetic**" because of similarities in small molecule transport, ionization selectivity, lipophilicity

Patrick Sinko et al.

Concluding Thoughts and Future Directives

- Centralized philosophy: we need *in vivo* data to optimize & validate *in vitro/in silico* models:
  - **The first study** in a large population of healthy volunteers (n=37), with aspiration of fluids at the different segments of the GI tract in parallel with monitoring motility events and systemic exposure

- **Science is a work in progress:** 21st Century BE/BA Studies

- **How complex do we need to go? What's the level of complexity?**

- **Future**: Multidisciplinary approach – **Combined *In Vivo* Techniques**

  ➔ MRI in combination with intubation studies

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John Duan – Pharmacologist
Hong Wen - Chemist
Dajun Sun – DQMM/ORS/OGD/CDER
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Hans Lennernäs (Uppsala, SE)

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Copenhagen, Denmark