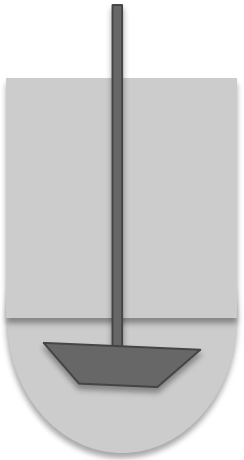
Advancing the Dissolution Toolbox in Drug Development: Novel Bio-predictive Dissolution Methodologies for Oral Products

4th FDA/PQRI Conference on Advancing Product Quality (April 9-11, 2019)



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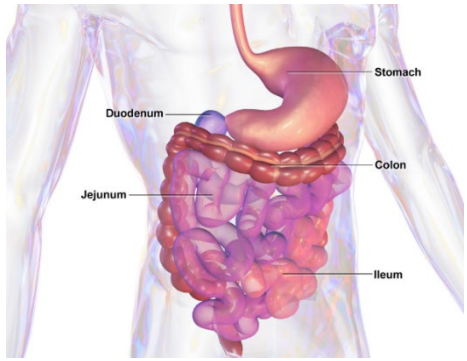

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- Nicholas Job — Graduate Student
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- Raimar Lobemberg — Visiting Professor
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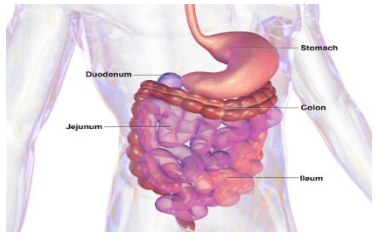
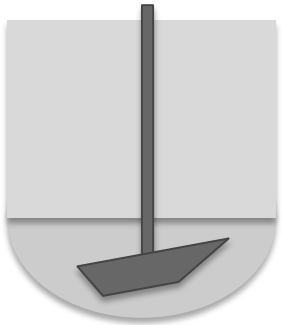
Bridging In Vitro and In Vivo studies for Oral Products.

GI Physiology is complex

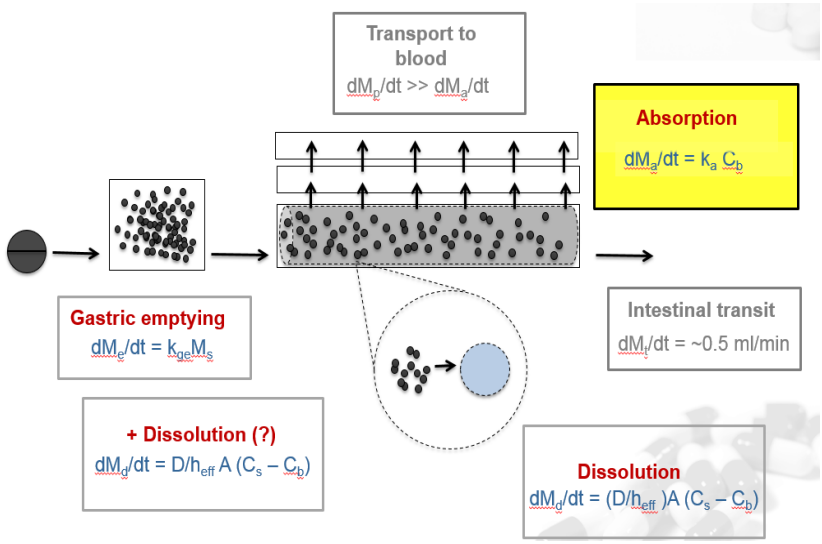


Including recent learnings from U-M Human intubation study sponsored by FDA (eg: stomach emptying, motility)

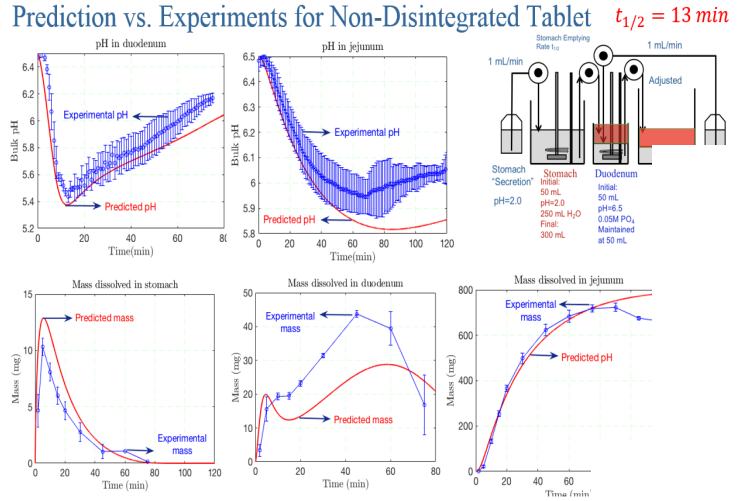
Standard industrial product dissolution tests are not



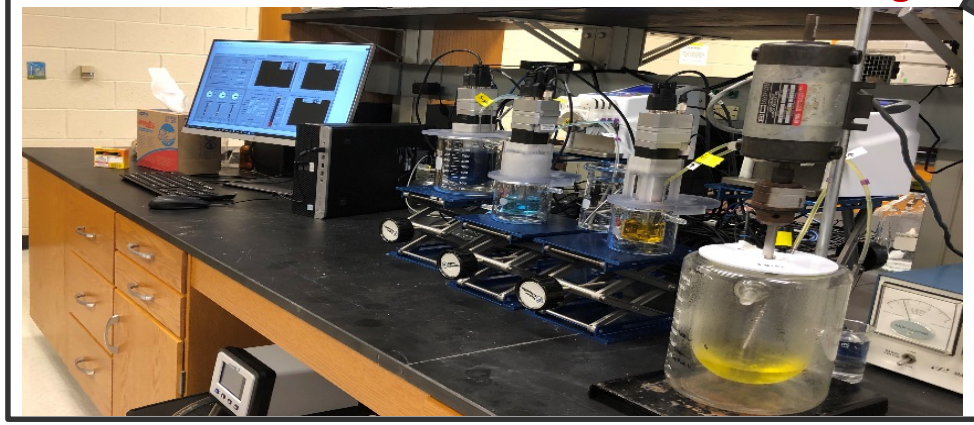
Goal: Integrate, physical chemistry and physiology



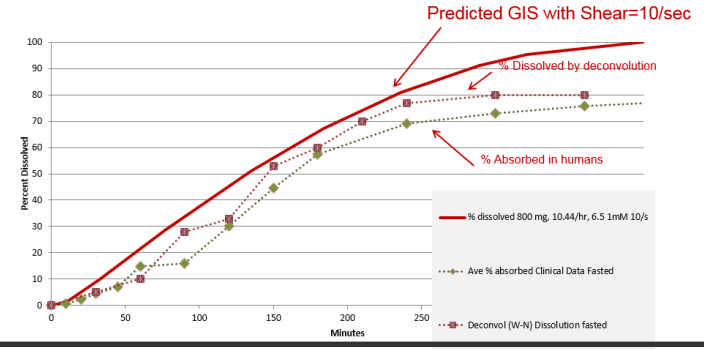
to predict what happens in the in vivo environment



with in vivo relevant dissolution methodologies



and relate in vitro results to in vivo performance.



Dissolution Testing: The Future

Need to transition to multiple dissolution methodologies for different purposes

- Quality control (eg: Good, Fast, and Cheap, for change control)
- In Vivo Predictive (eg: not necessarily Fast or Cheap, for QbD purposes)

In vivo Predictive Dissolution (IPD) should:

- Be physiologically relevant
- Consider drug properties: (acid, base, neutral)
- Utilize appropriate dissolution methodology from several options (no less, no more)
  - Current compendial methods (eg: Apparatus 1, 2, 3, 4)
  - Multicompartment systems: Gastrointestinal Simulators (eg: ASD, GIS, TIM)
  - Multiphase systems to simulate absorption: (eg: Biphasic, polymer membrane systems)
  - pH – Dilution methods
  - Other?

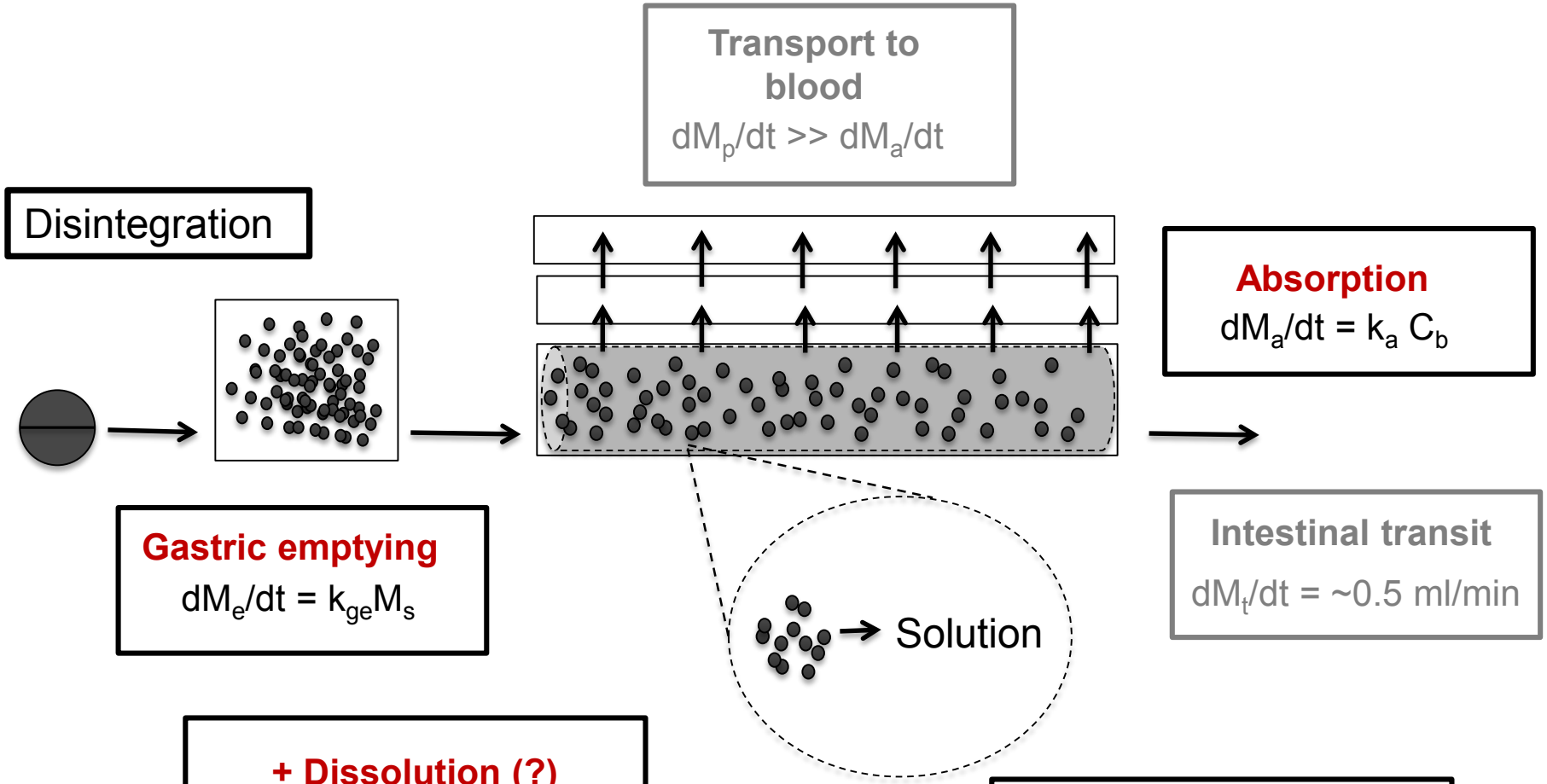
Novel In vitro systems in the literature

Curtesy Randy Wald*, Elke Lipka*, Gordon Amidon*+ (*TSRL, U-M+)

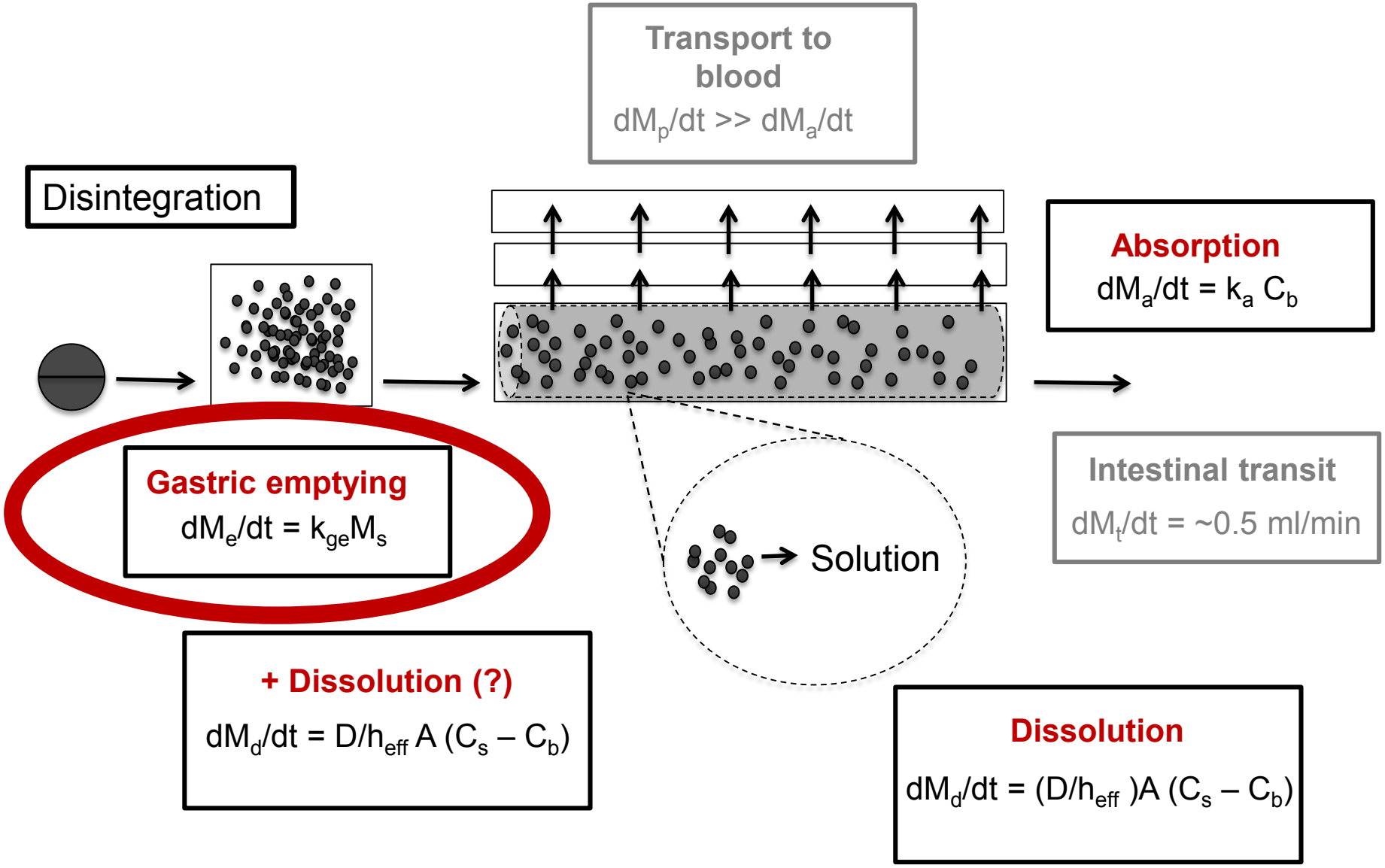
Gastrointestinal Simulator: GIS 2.0

GIS1.0

Goal: Integrate physical chemistry and physiology into a dissolution system that is kinetically relevant



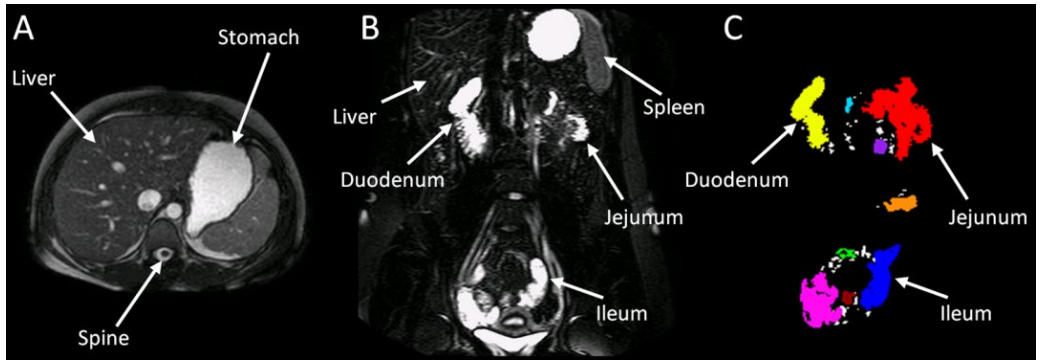
Goal: Integrate physical chemistry and physiology into a dissolution system that is kinetically relevant



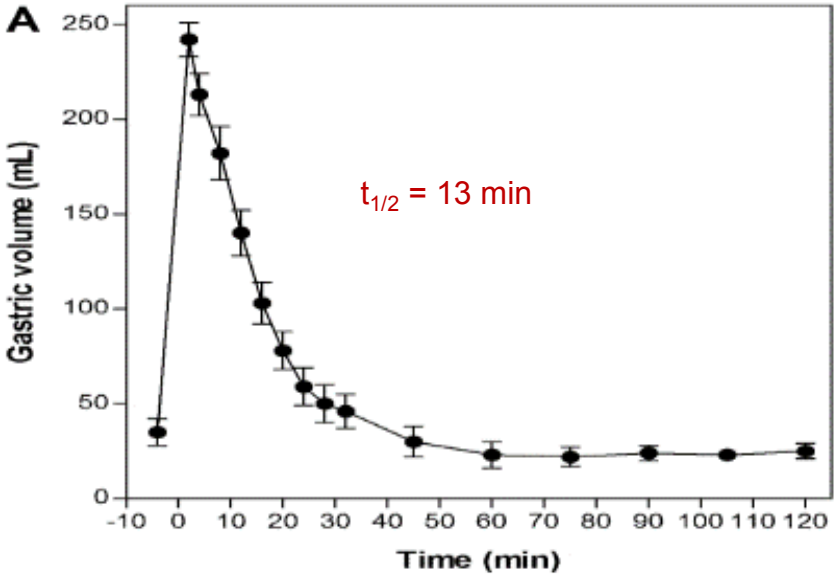
Intestinal Water Content (by MRI)

Fasted state
240 mL water dose

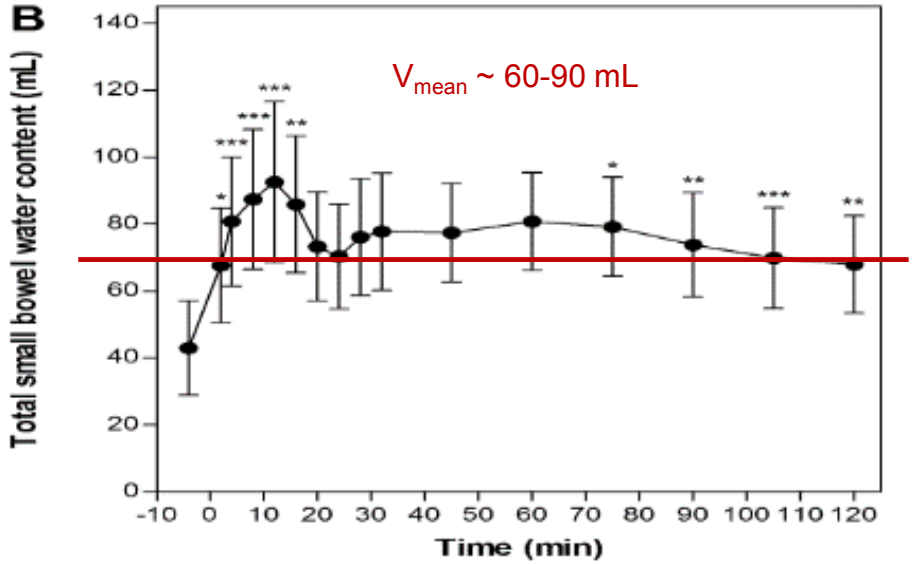
MRI in healthy volunteers



Liquid contents of the: stomach (Fig. 3A), small bowel (Fig. 3B), multiple intensity projection image of individual small bowel water pockets, colour coded and extracted from images (Fig. 3C) .



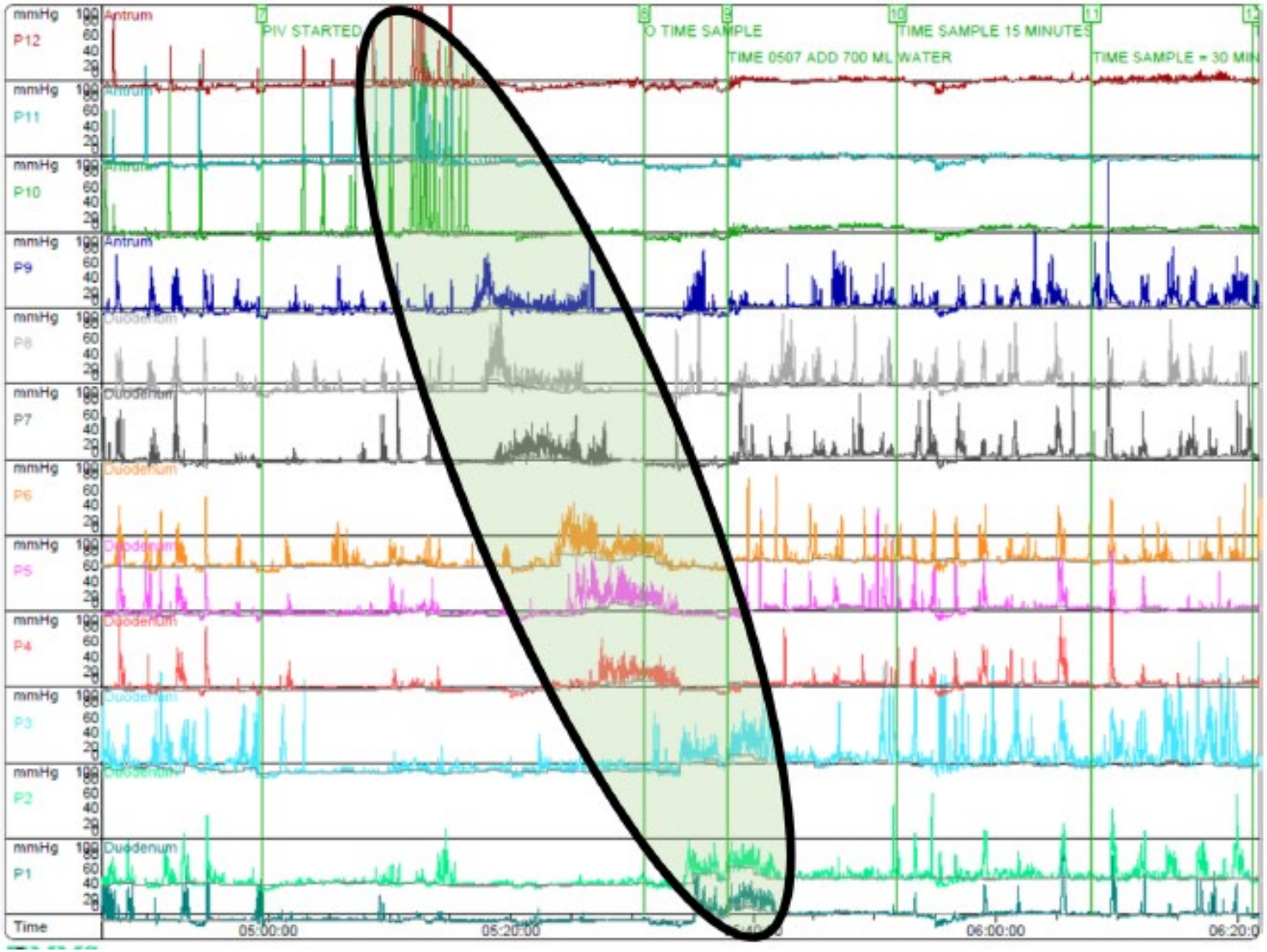
Mean Gastric Volume before and after 240 mL



Mean Total Intestine Water Content before and after 240 mL

DMMudie,..,LMarciani. Molecular Pharmaceutics. 11:3039-3047 (2014).

GI Motility (Subject B049, visit 2)

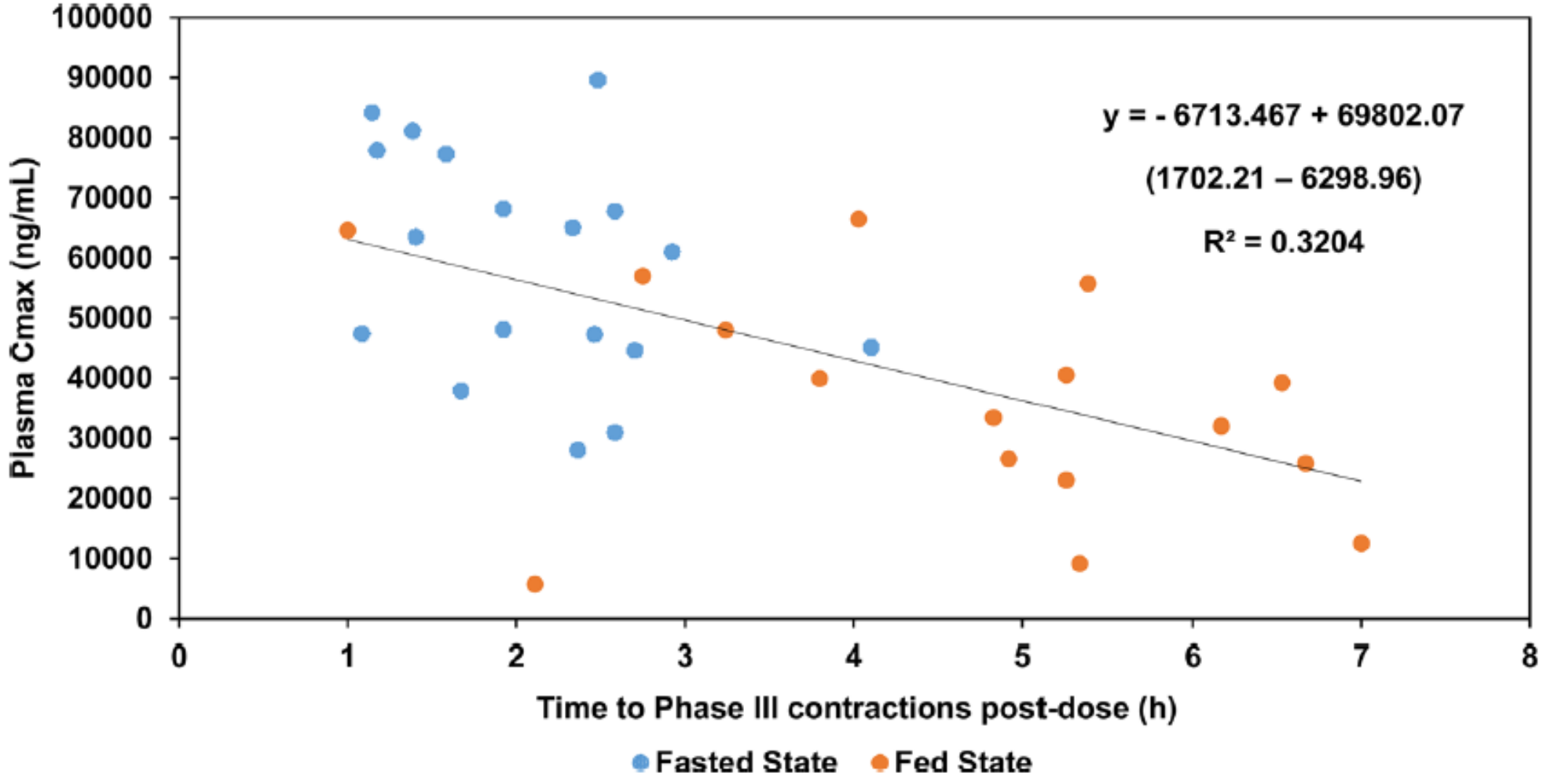


Gastric Antrum Phase III activity

Distal intestinal segments

B. Hens, Y. Tsume, M. Bermejo, etal. Low Buffer Capacity and Alternating Motility along the Human Gastrointestinal Tract: Implications for in Vivo Dissolution and Absorption of Ionizable Drugs. Molecular Pharmaceutics. 14:4281-4294 (2017).

Plasma Cmax versus Time to Phase III Contractions



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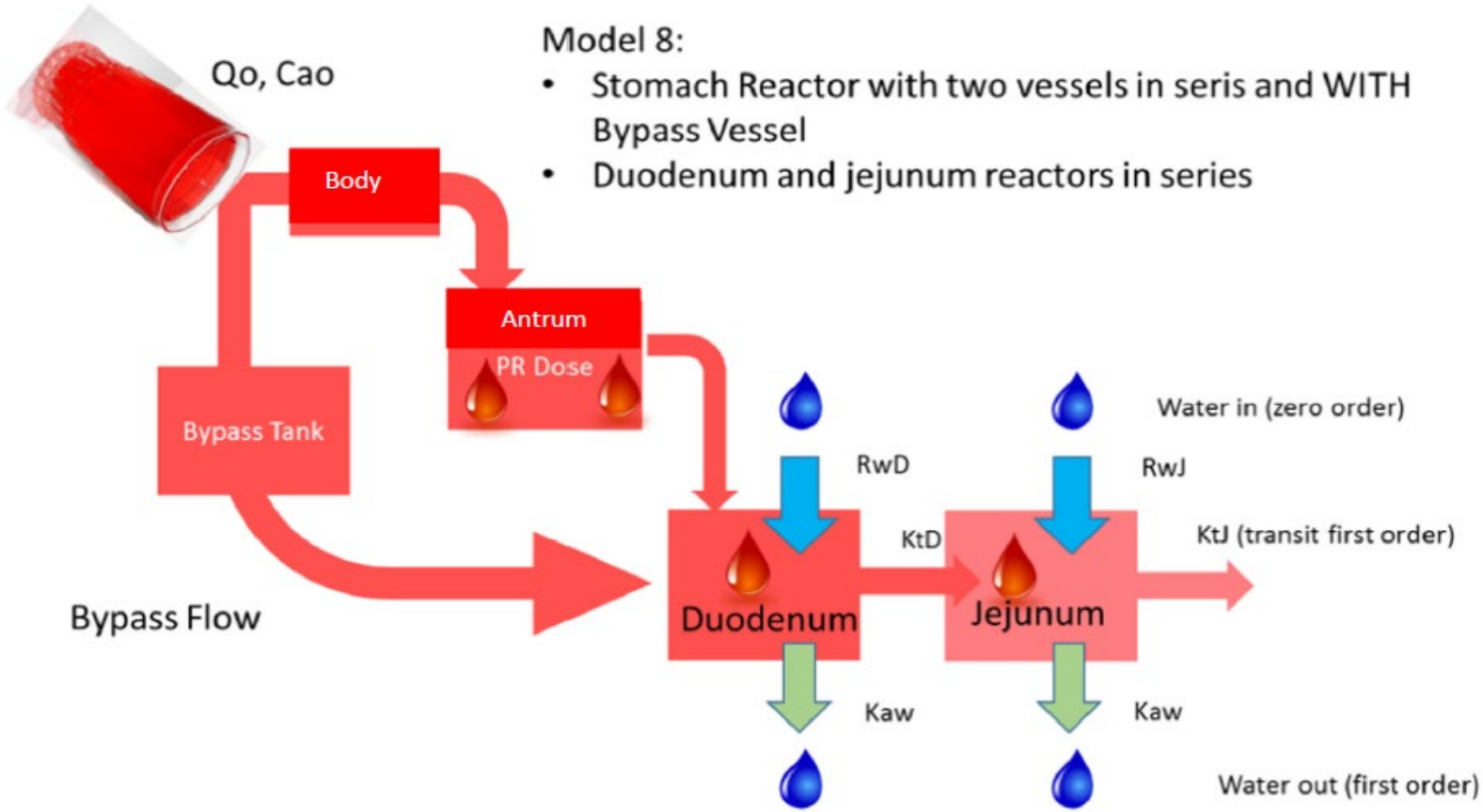
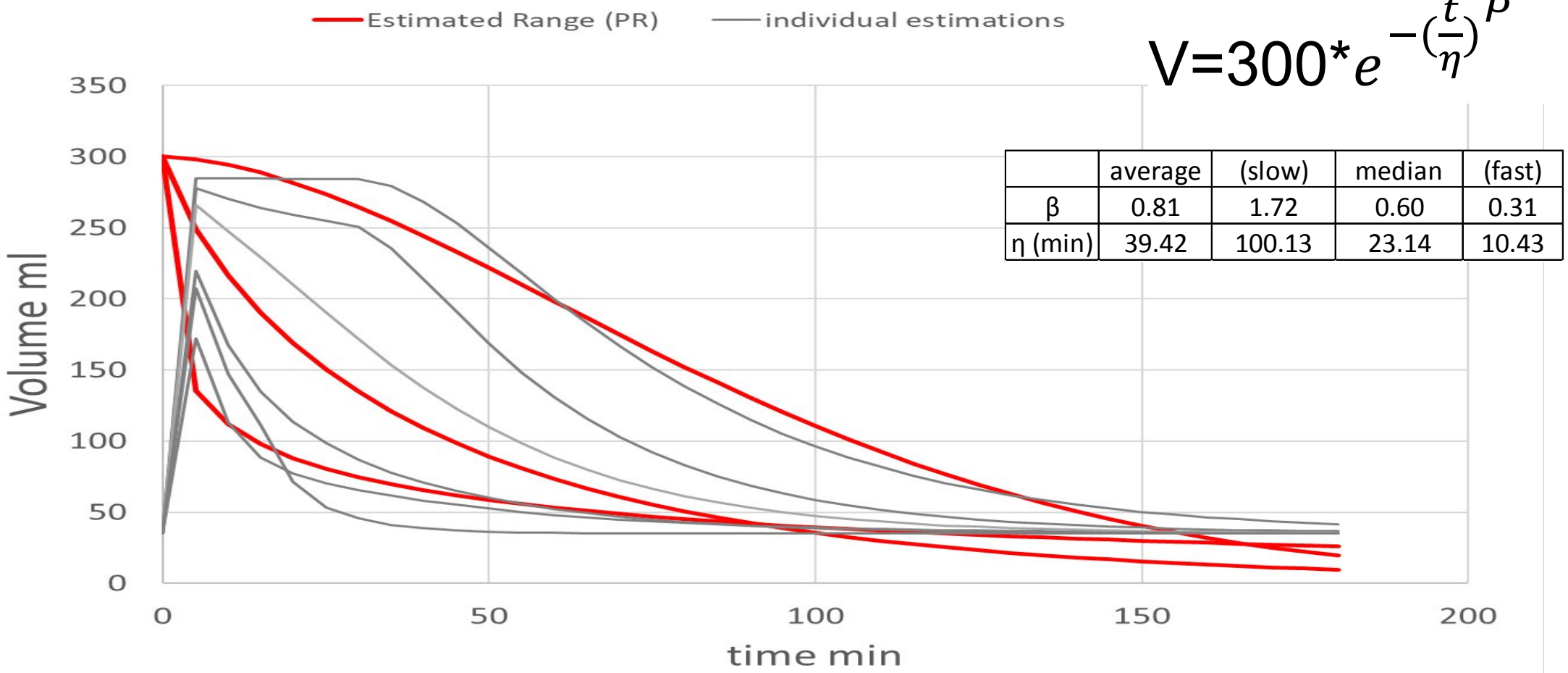
Gastric Emptying (The gateway to drug absorption)



P. Paixao, M. Bermejo, B. Hens, Y. Tsume, etal. Gastric emptying and intestinal appearance of nonabsorbable drugs phenol red and paromomycin in human subjects: A multi-compartment stomach approach. Eur J Pharm Biopharm. 129:162-174 (2018).

Gastric Emptying (Weibull approximation)



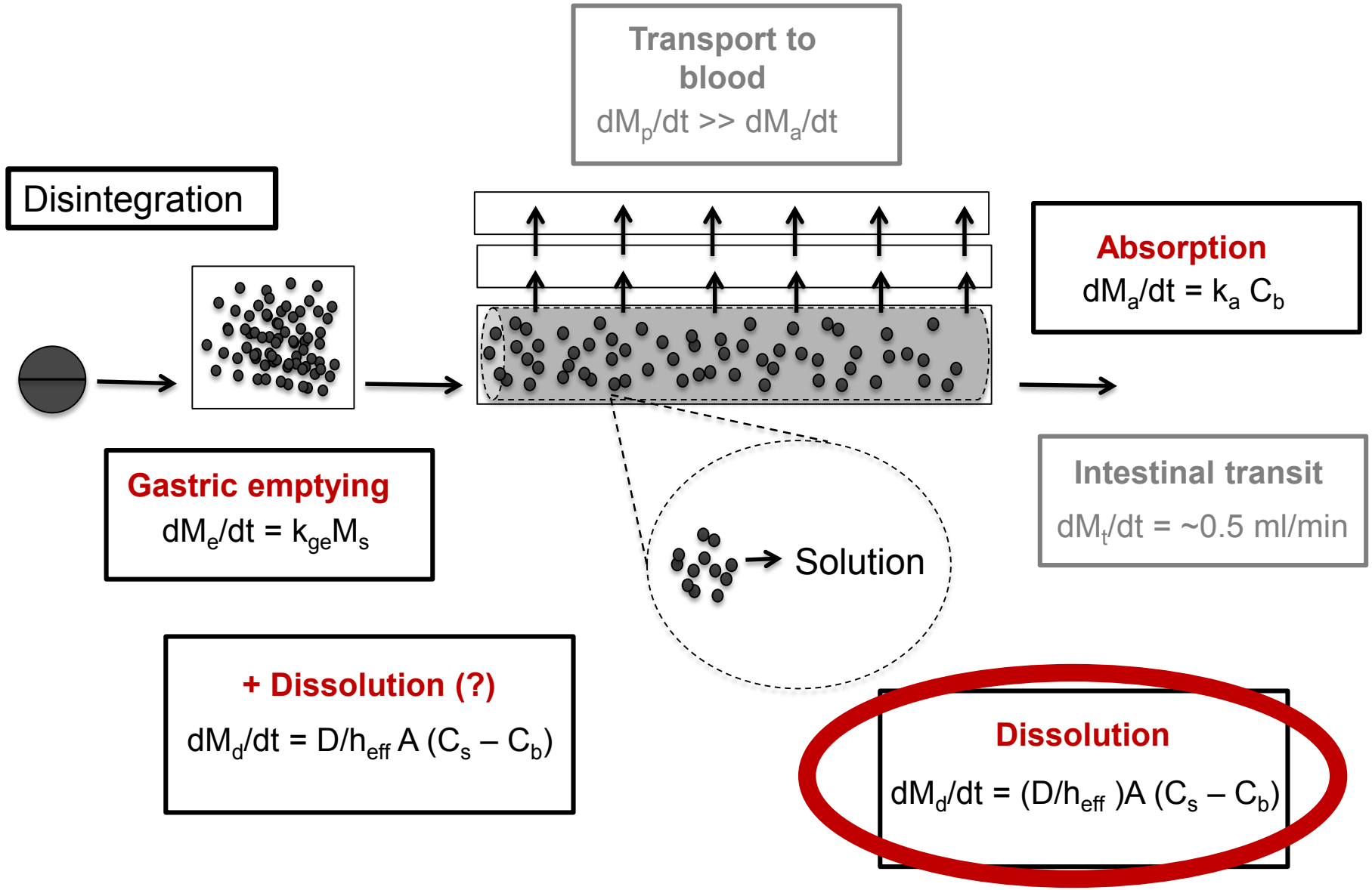
$$V=300*e^{-\left(\frac{t}{\eta}\right)^{\beta}}$$

	average	(slow)	median	(fast)
β	0.81	1.72	0.60	0.31
η (min)	39.42	100.13	23.14	10.43

Reference:

- Marival Bermejo. Personal Communication
- P. Paixao, M. Bermejo, B. Hens, Y. Tsume, etal, Eur J Pharm Biopharm. 129:162-174 (2018).

Goal: Integrate physical chemistry and physiology into a dissolution system that is kinetically relevant



Dissolution media

Bicarbonate buffer is the primary buffer of the intestinal tract and in fact of all biology

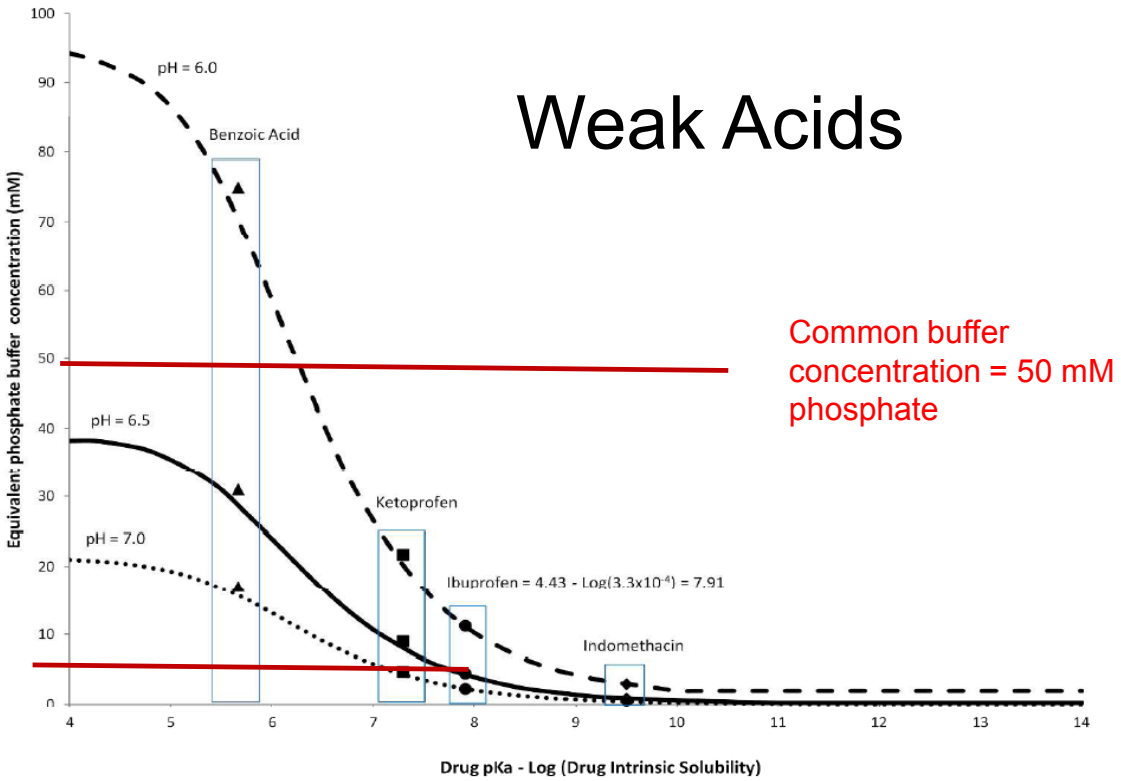
It has interesting properties that have important biological and drug delivery implications

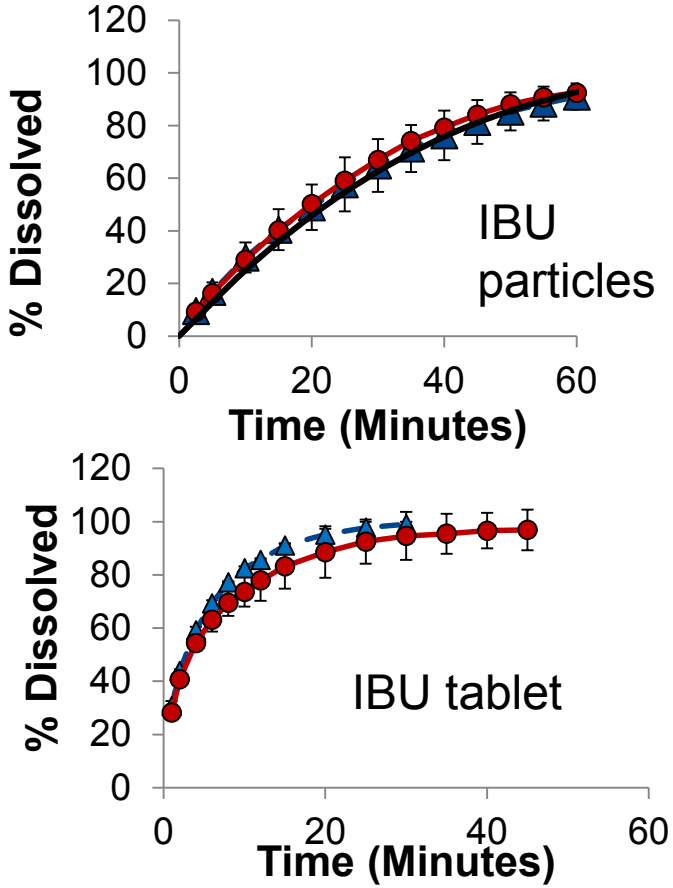
- Complex, unconventional buffer behavior
- Low in vivo buffer capacity

Phosphate Buffer to Equivalent 15% CO_2 @ pH=6, 6.5, 7 (10.4 mM HCO_3^-)

At the dissolving drug surface: $CO_2(aq) + H_2O \overset{k_d}{\leftarrow} H_2CO_3 \overset{K_1}{\rightarrow} H^+ + HCO_3^-$ $k_h \equiv 0$ **

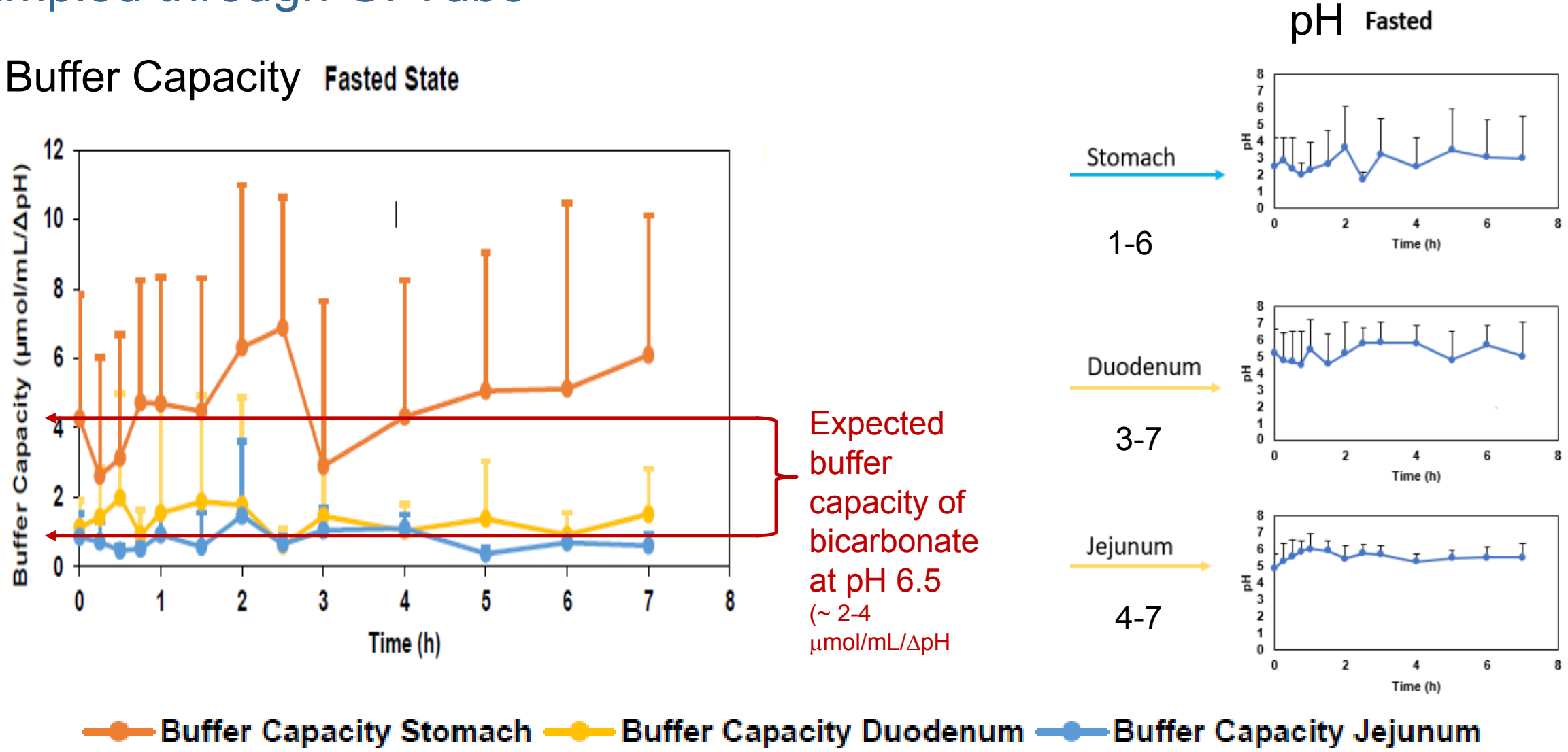
In the bulk liquid: $CO_2(aq) + H_2O \overset{K_0}{\rightarrow} H_2CO_3 \overset{K_1}{\rightarrow} H^+ + HCO_3^-$ k_d and $k_h \equiv$ Instantaneous





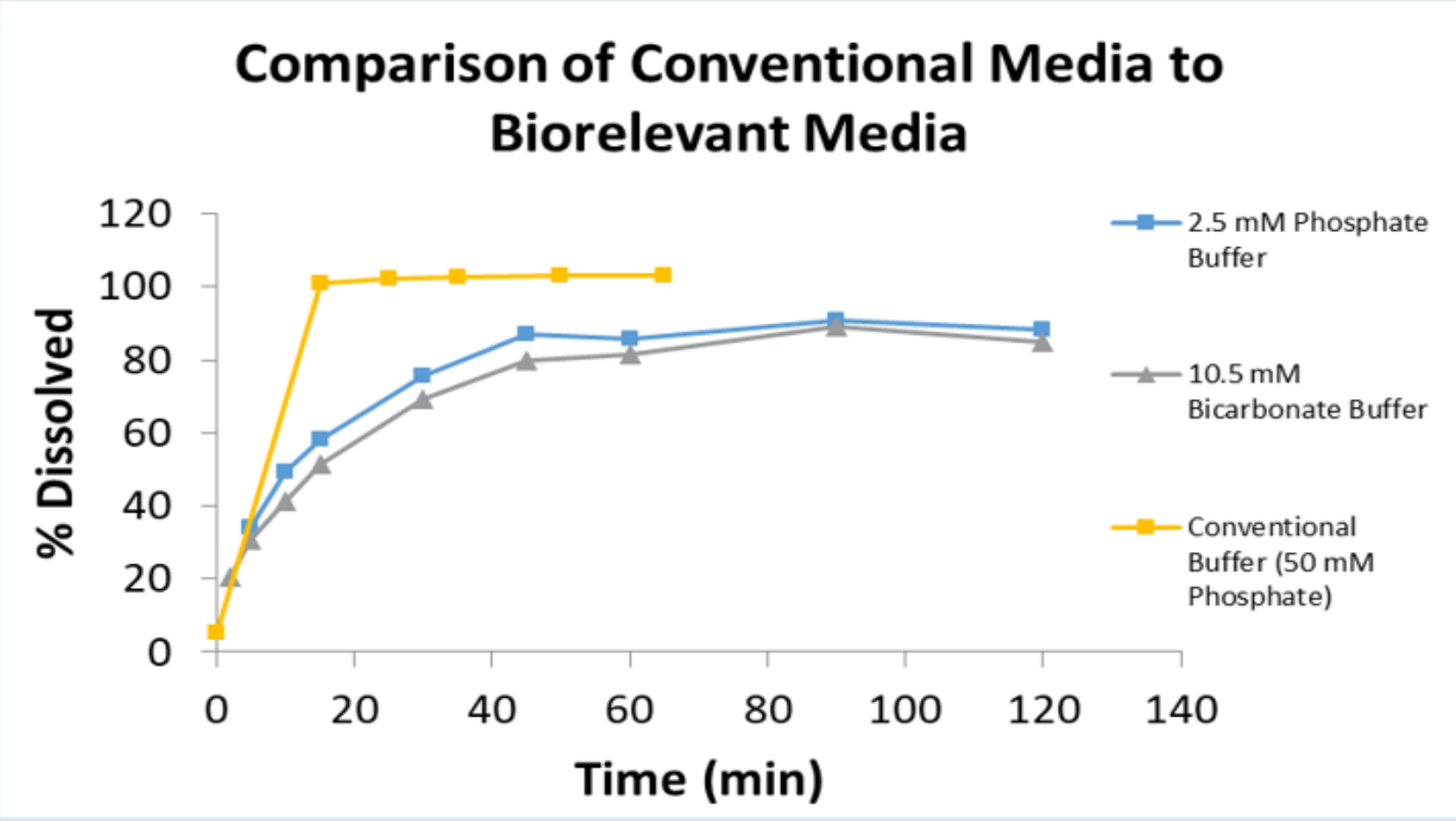
Reference: B.J. Krieg, etal. Journal of Pharmaceutical Sciences. 104:2894-2904 (2015)
** J. Al-Gousous, N. Salehi, , etal. Work in progress.

In Vivo Buffer Capacity and pH: Humans Fasted State (800mg Ibu) Sampled through GI Tube



Ref: B. Hens, etal. Low Buffer Capacity and Alternating Motility Along The Human Gastrointestinal Tract: Implications for in vivo Dissolution and Absorption of Ionizable Drugs. Accepted Molecular Pharmaceutics (2017).

Bicarbonate buffer dissolution. Equivalent phosphate (2.5 mM phosphate @ pH =7.0) HPMCAS (enteric) granules



Ref: N. Job, G.E. Amidon, W. Forrest, A. Hermans, and S. Patel. Evaluation of Compound A Amorphous Solid Dispersion Dissolution in in Vivo Relavant Dissolution Media, *AAPS PharmSci360*, Washington DC, 2018.

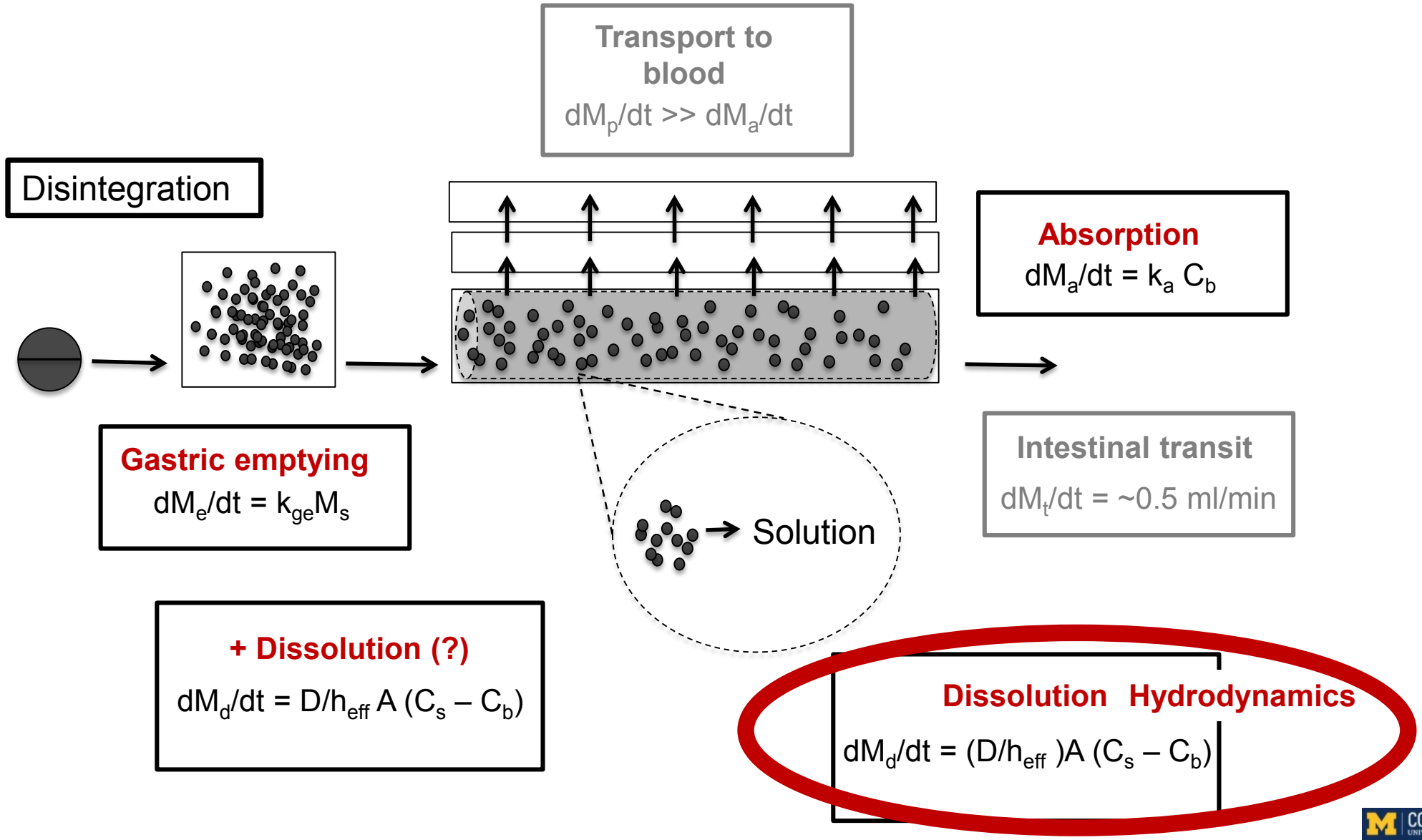
Physiologically relevant conditions we now know better…

- Stomach emptying rate ($t_{1/2}$ ~ 13 min, complex, dependent on GI motility state)
- Buffer concentration (low, 5-15 mM bicarb, lower for PO4)
- Buffer type (bicarbonate, or equivalent phosphate?)
- pH (stomach: 1-5, duodenum: 3-6, jejunum: 5-7)
- Fluid volume (60-90 mL in small intestine)

What about:

- Hydrodynamics?
- Absorption?

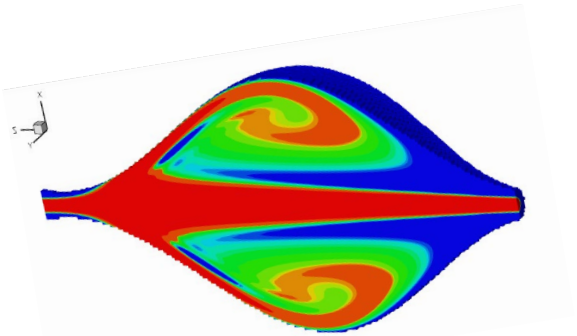
Goal: Integrate physical chemistry and physiology into a dissolution system that is kinetically relevant

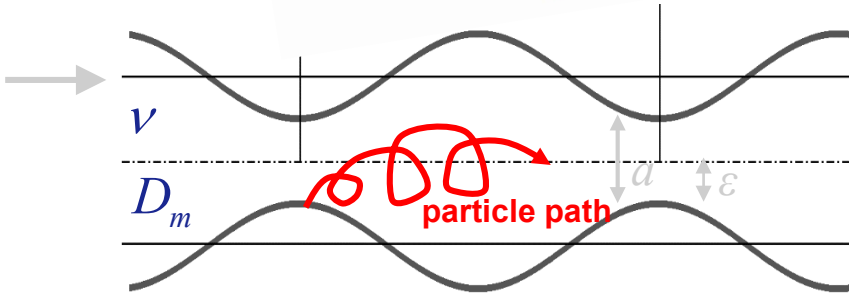


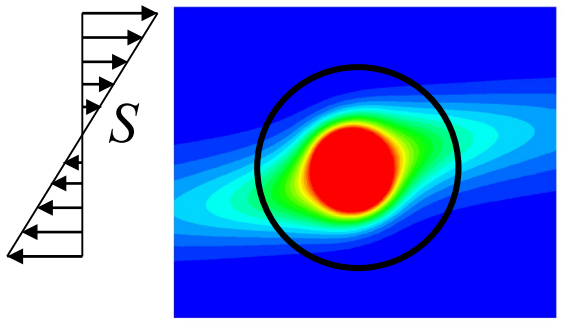
Hydrodynamic Parameters that Govern In Vitro and In Vivo Dissolution

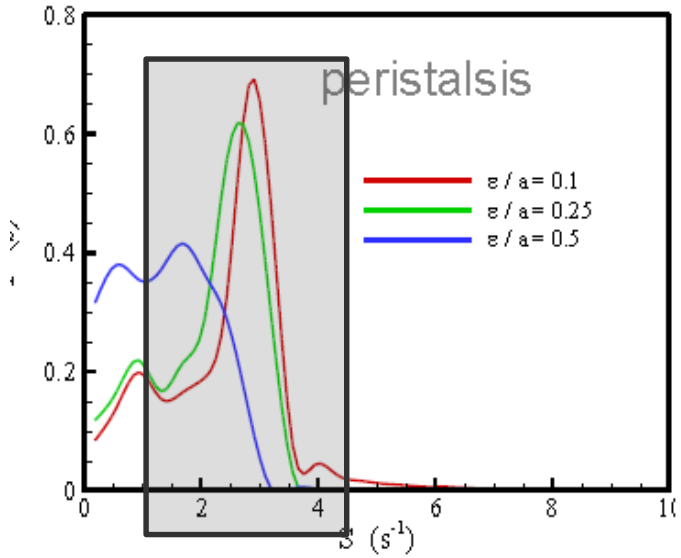
(Yanxing Wang, James Brasseur (UColorado)

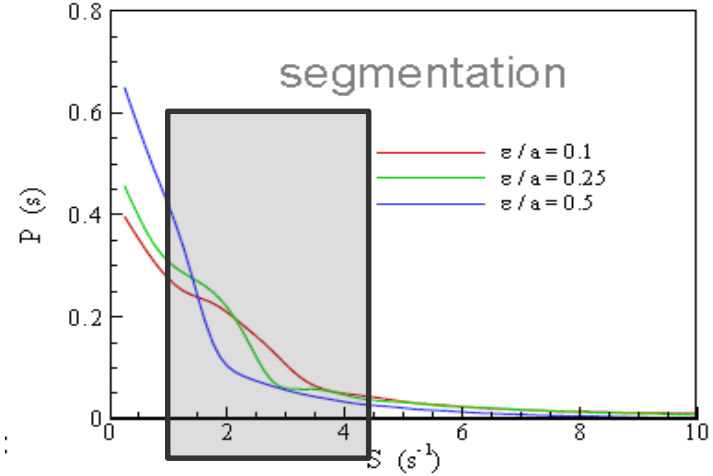
Model Intestinal fluid flow











Simulations of Shear in Intestine: JBrasseur, etal

Particle dissolution:

Higuchi-Hiestand (pure diffusion)

$$\frac{dm}{dt} = -D \cdot (4\pi a)(C_s - C_b)$$

To account for hydrodynamic effects:

Sh = Sherwood number

= normalized surface flux

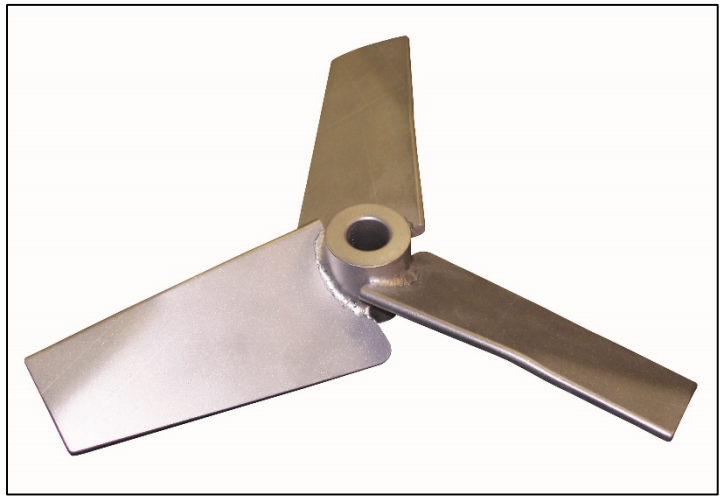
$$Sh = (1 + \Delta_{shear} + \Delta_{convection} + \ldots)$$

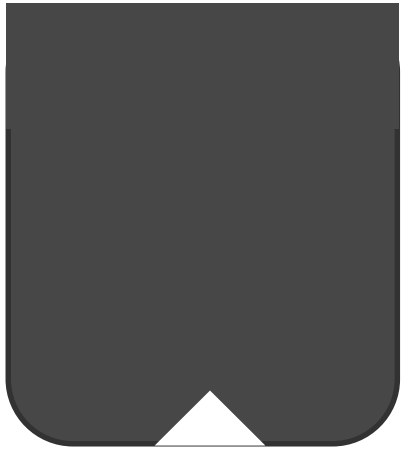
$$\frac{dm}{dt} = -Sh \cdot D \cdot (4\pi a)(C_s - C_b)$$

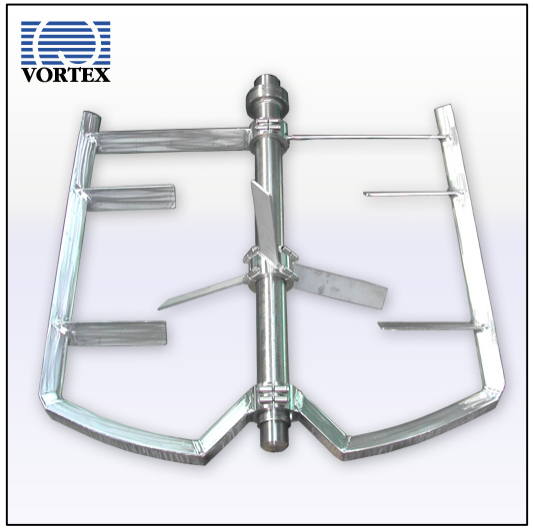
When Sh = 1 ⇒ pure diffusion

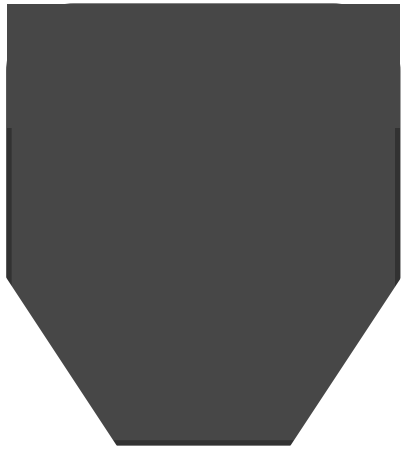
Sh > 1 with shear and convection are present

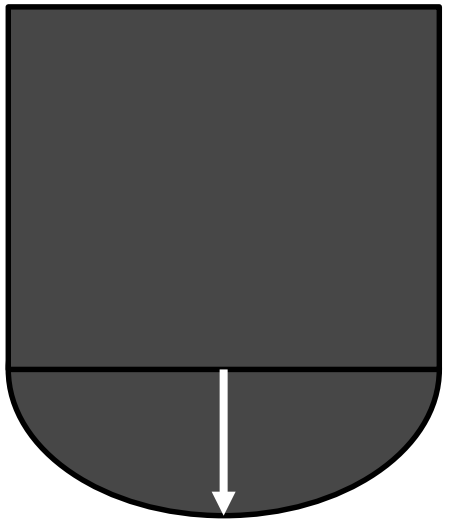
Selection of Impeller (Hydrofoil) Types and Vessel Shapes Considered
Goal: Physiologically relevant shear rates and well mixed









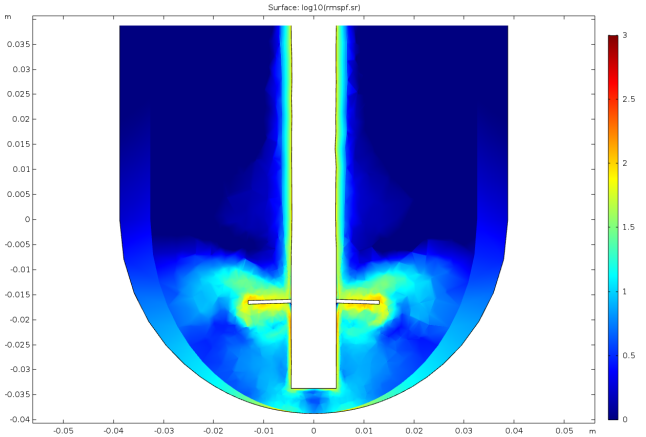


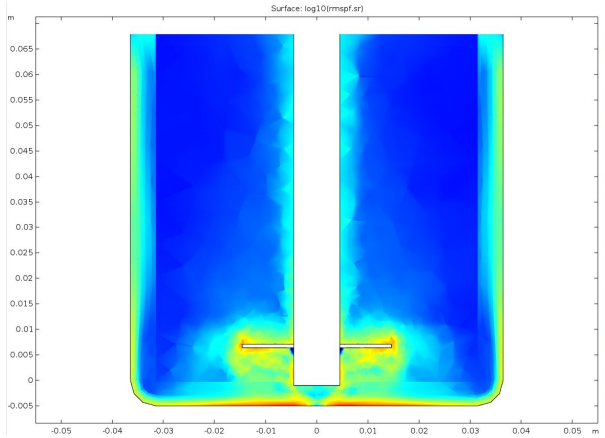
Images via Google Images
Graphic via Thermopedia.com “Mixers”

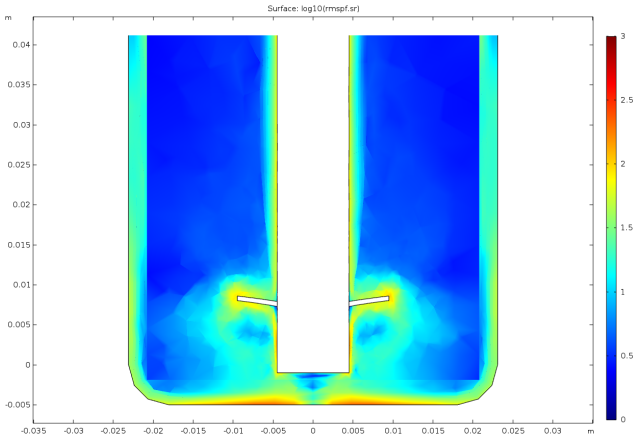
Stirrer (hydrofoil) and vessel design examples.
Goal: Achieve desired shear rates (maybe: Sherwood numbers (Σ convection + shear)

Compartment	300mL Dish Stomach @ 100RPM	300mL Flat Vessel @ 125RPM	75mL Duodenum & Jejunum @ 125RPM
Vol. Avg. SR [s^{-1}]	3.36	9.3	10.55

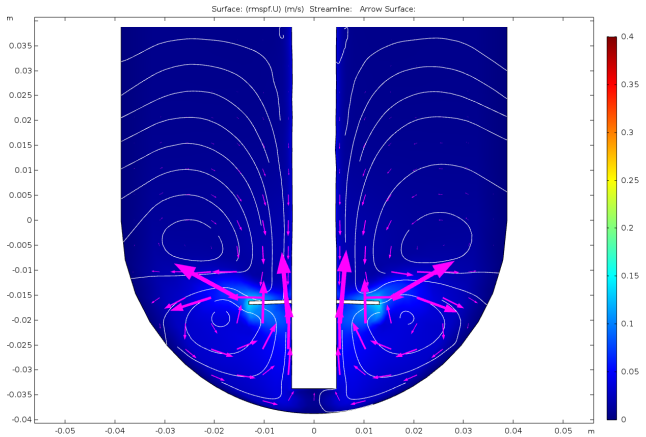
Log(shear rate)
Log[s^{-1}]

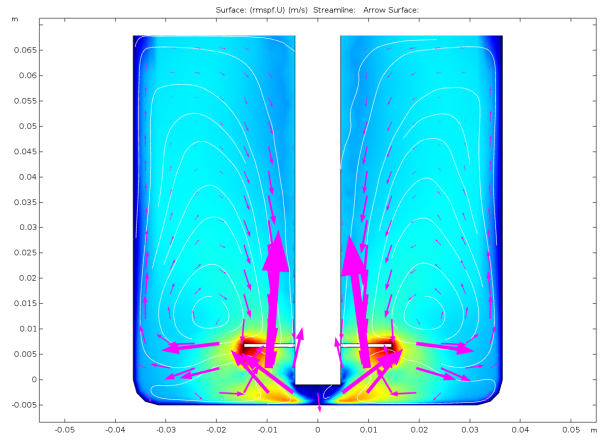


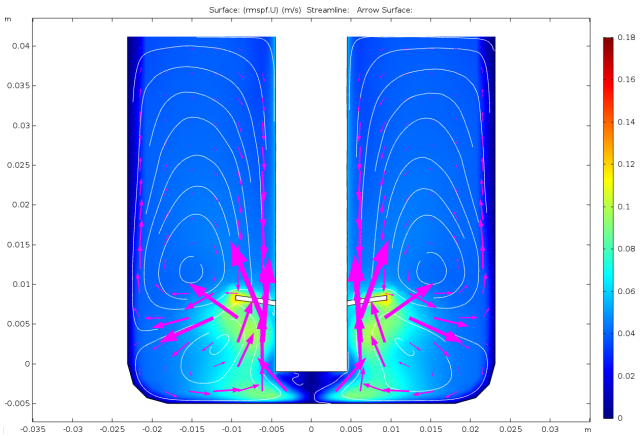




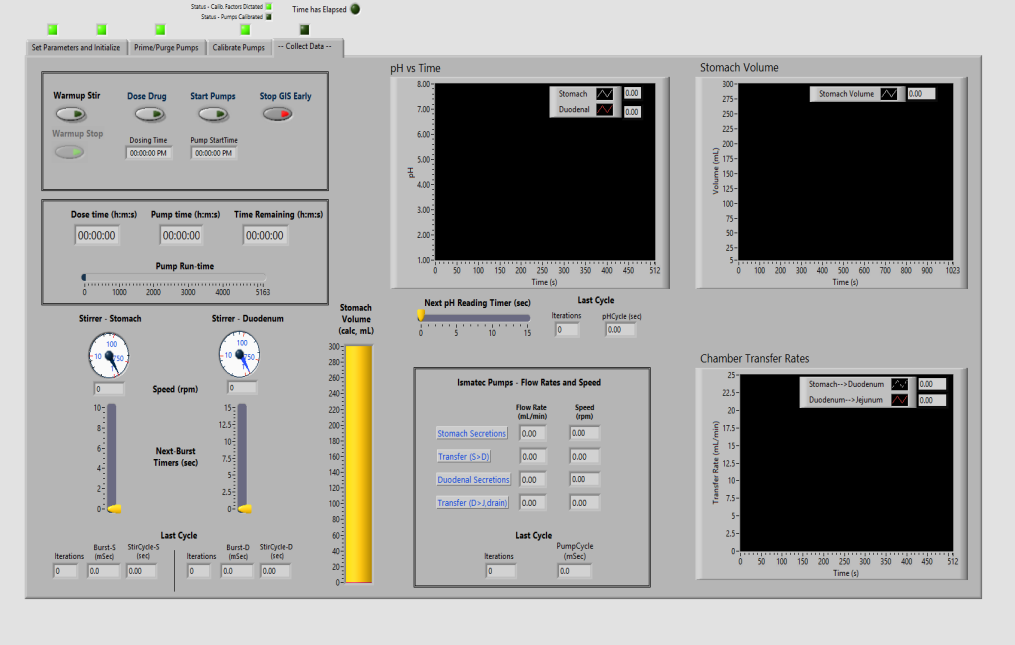
Velocity Profile
[ms^{-1}]

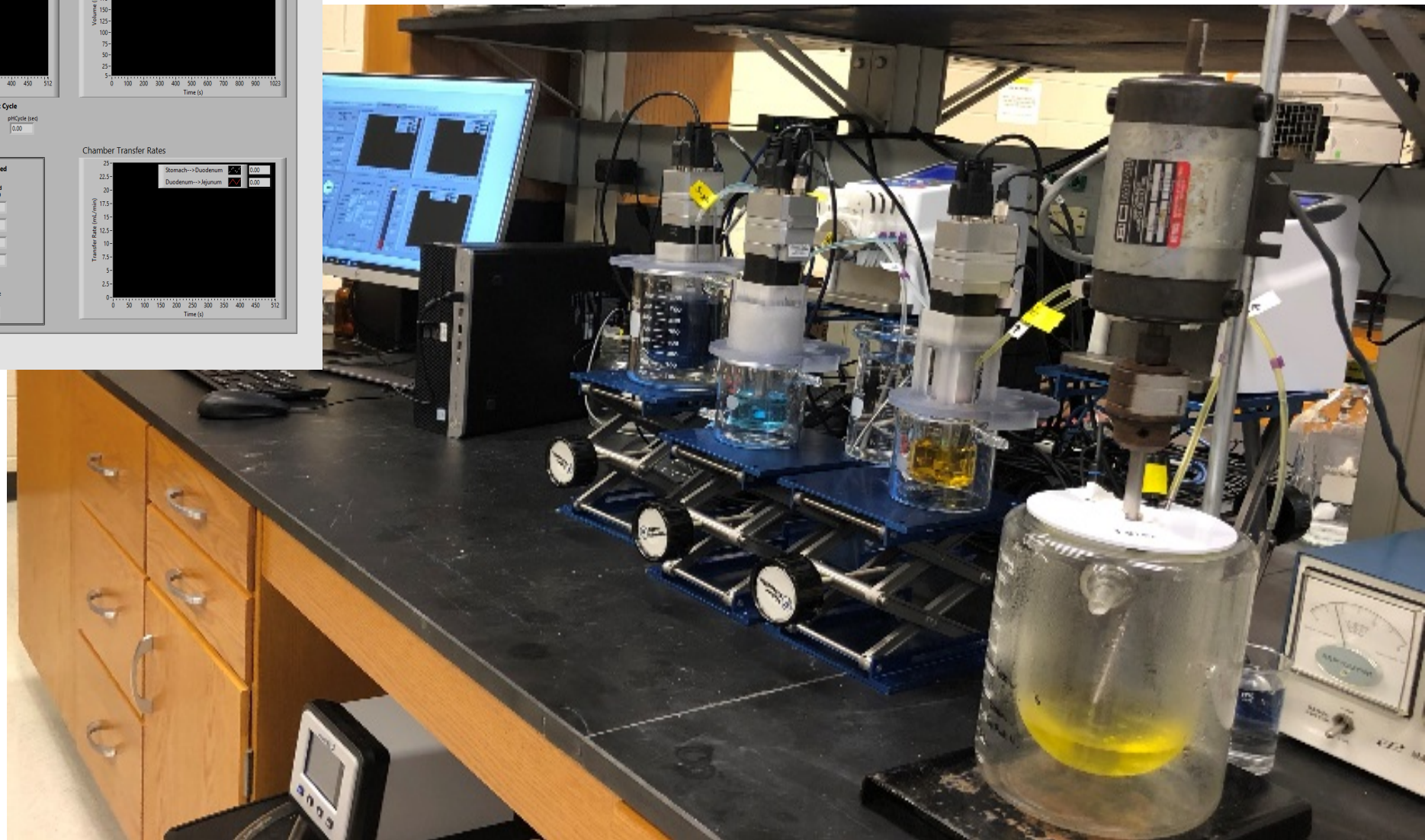




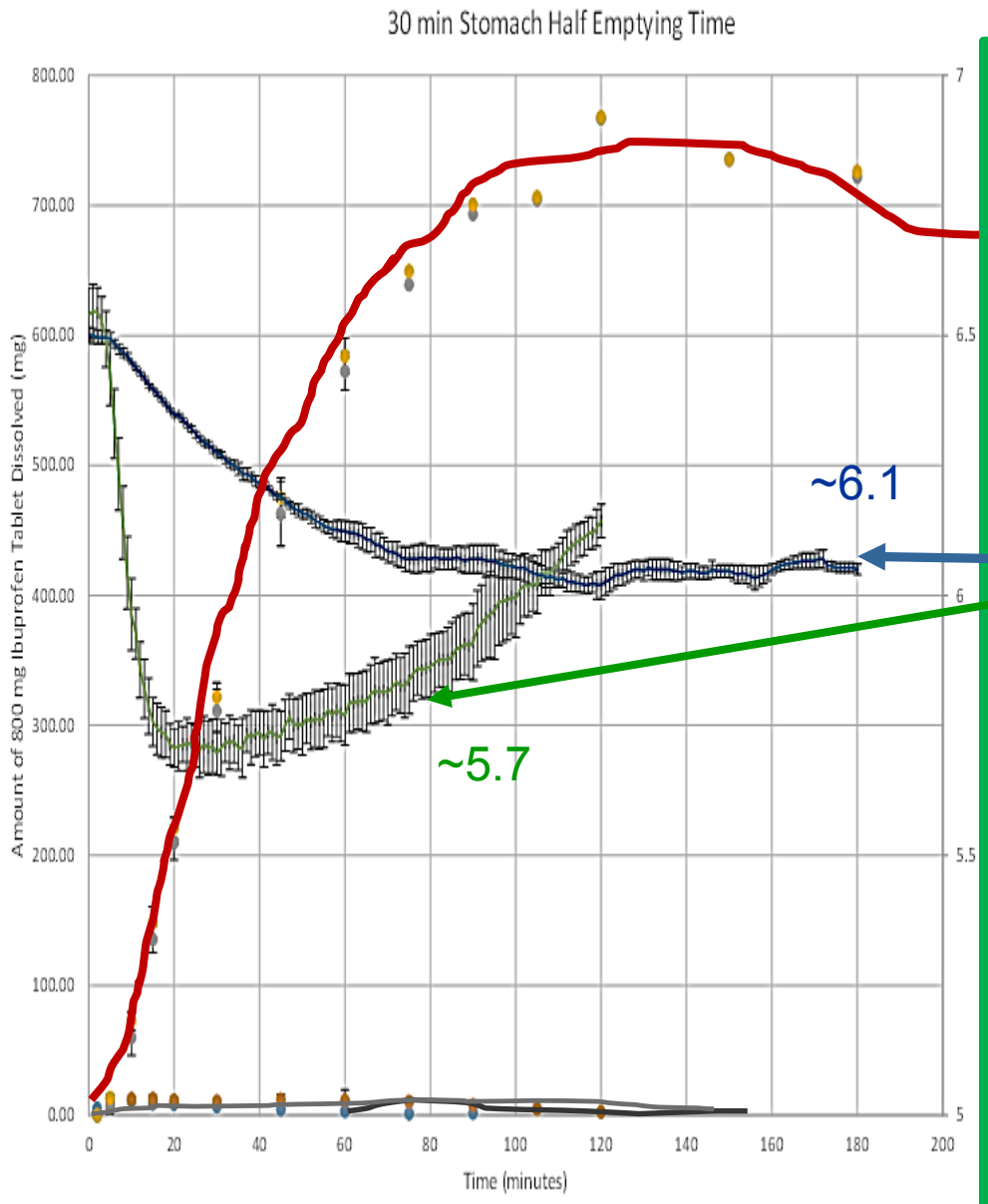


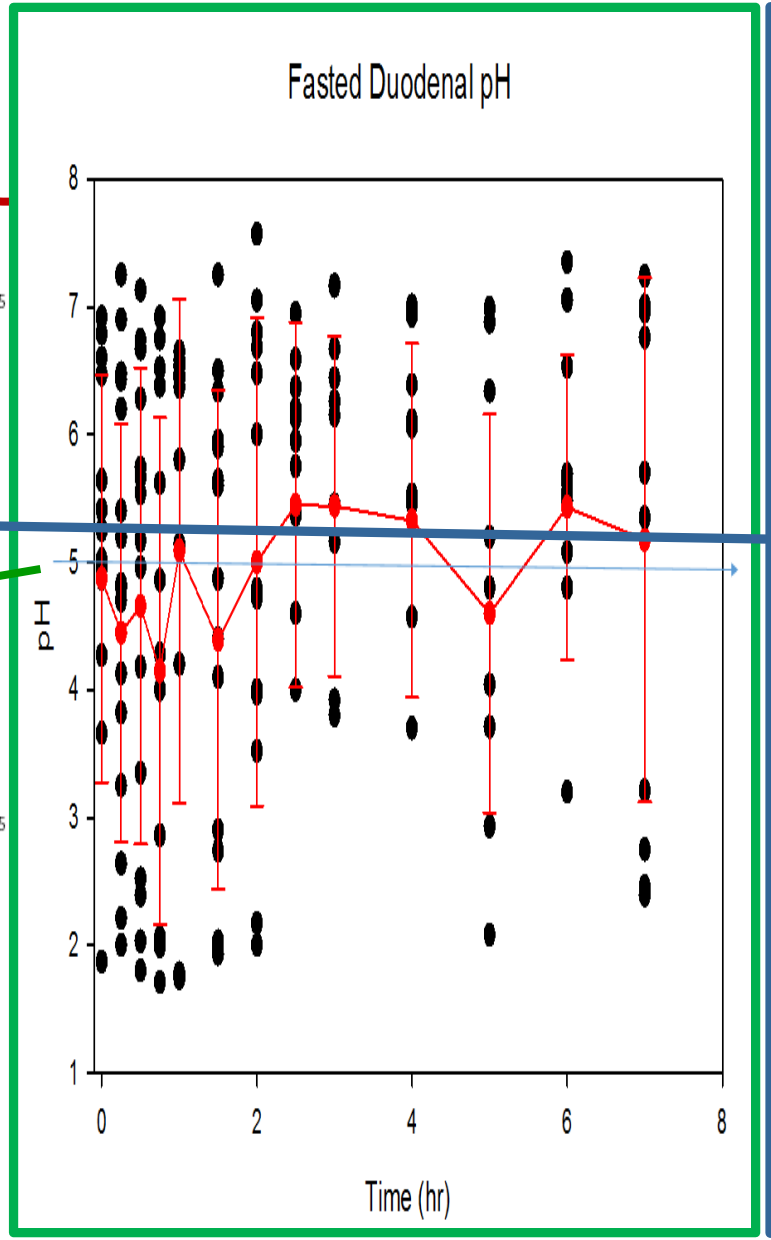
GIS Device

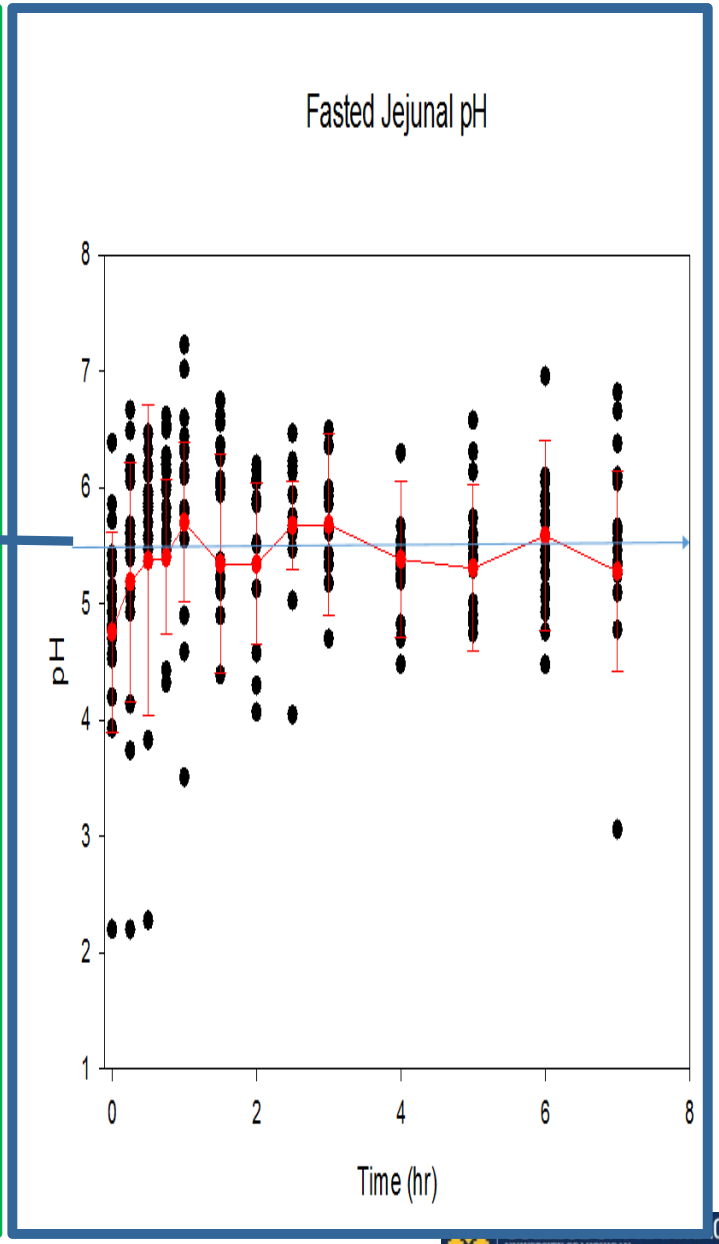

Set Parameters and Initialize
Prime/Purge Pumps
Calibrate Pumps
-- Collect Data --
Warmup Stir
Dose Drug
Start Pumps
Stop GIS Early
Warmup Stop
Dosing Time
Pump StartTime
Dose time (h:m:s)
Pump time (h:m:s)
Time Remaining (h:m:s)
Pump Run-time
Stirrer - Stomach
Stirrer - Duodenum
Speed (rpm)
Next Burst Timers (sec)
Last Cycle
Stomach Volume (calc, mL)
pH vs Time
Stomach
Duodenal
Next pH Reading Timer (sec)
Last Cycle
Ismatec Pumps - Flow Rates and Speed
Flow Rate (mL/min)
Speed (rpm)
Stomach Secretions
Transfer (S>D)
Duodenal Secretions
Transfer (D>),drain)
Last Cycle
PumpCycle (mSec)
Stomach Volume
Chamber Transfer Rates
Stomach-->Duodenum
Duodenum-->Jejunum
Transfer Rate (mL/min)
Time (s)



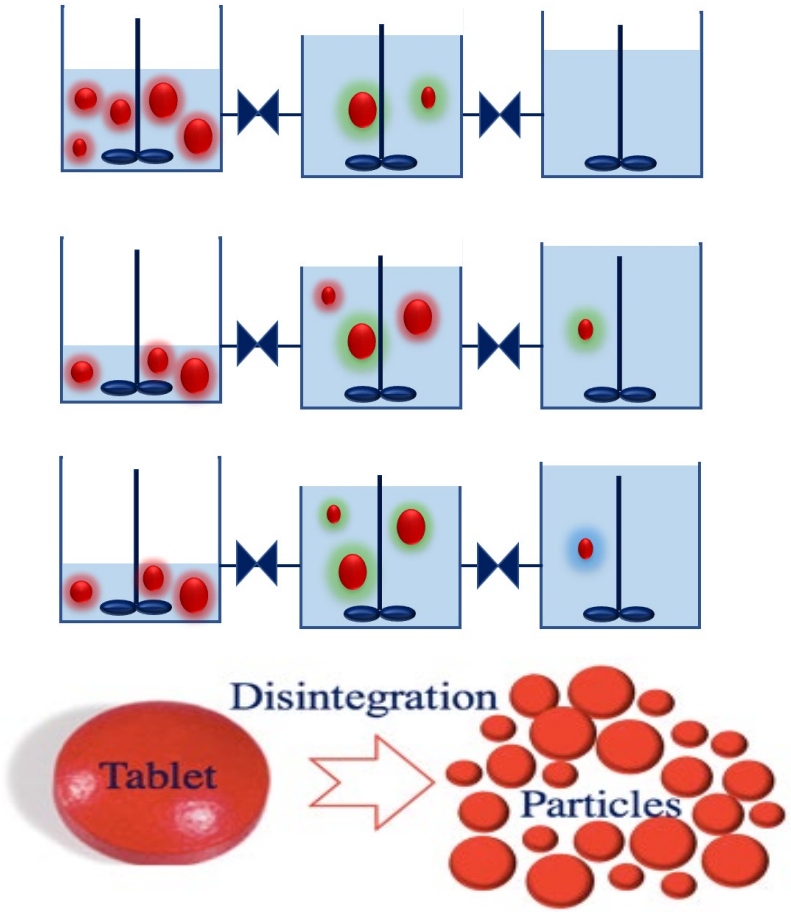
GIS1 Compared with in vitro & in vivo pH results

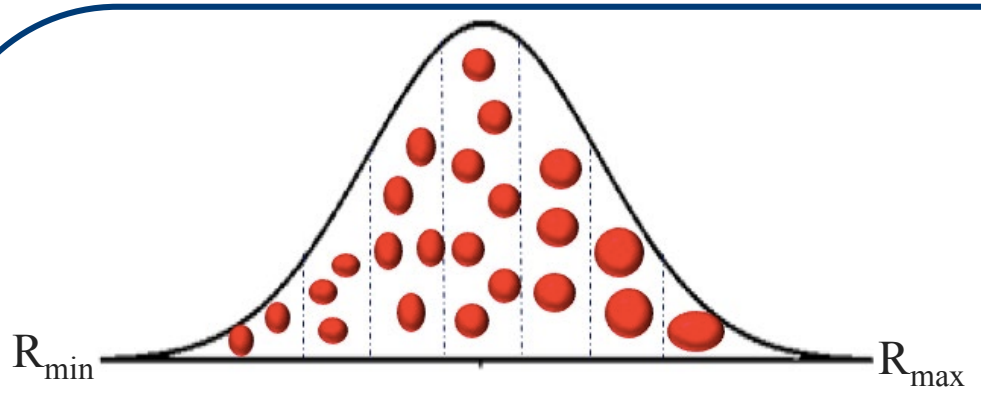






Mass Transport Analysis of GIS (and In Vivo environment)





$$\frac{dR_j(t)}{dt} = -\nu_m D \frac{C_s(t) - C_b(t)}{R_j(t)} Sh_j(t)$$

$C_s(t)$: Solubility

$C_b(t)$: Bulk concentration

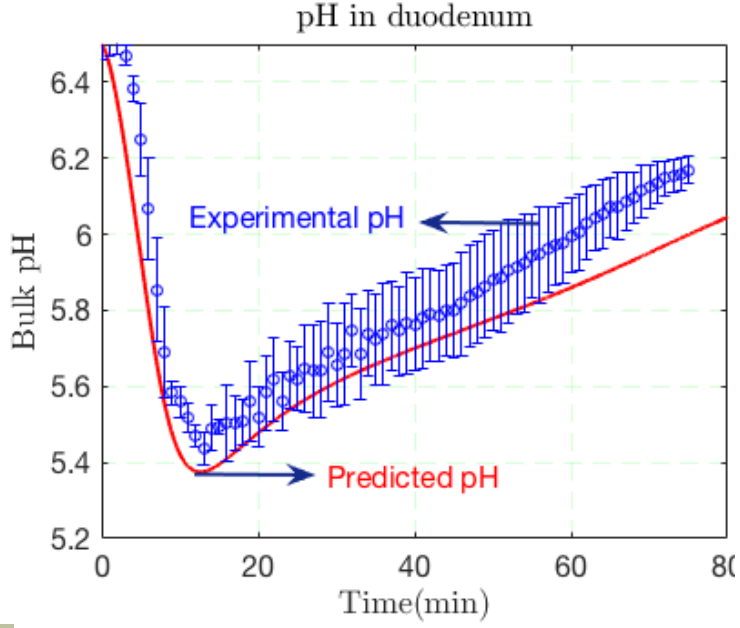
ν_m: Molar volume of the drug

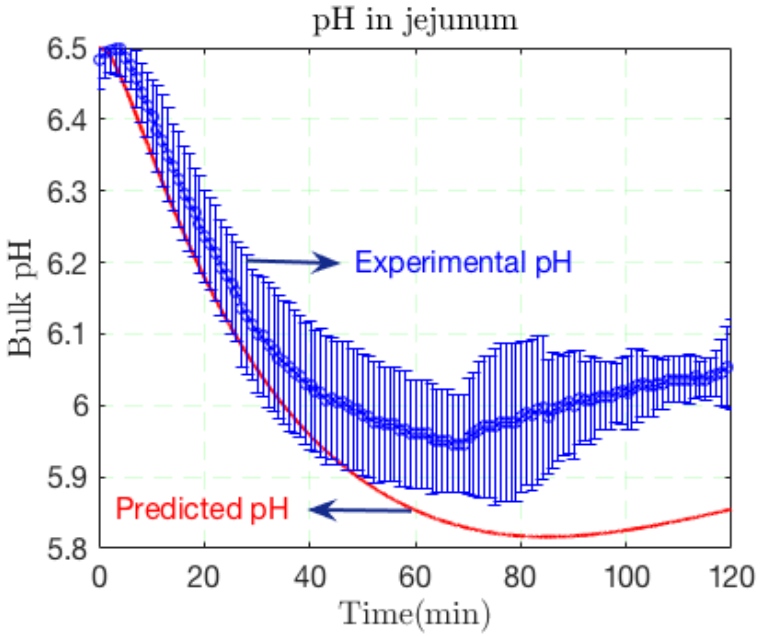
D: Diffusion coefficient of drug molecules

R_j: Radius of particle

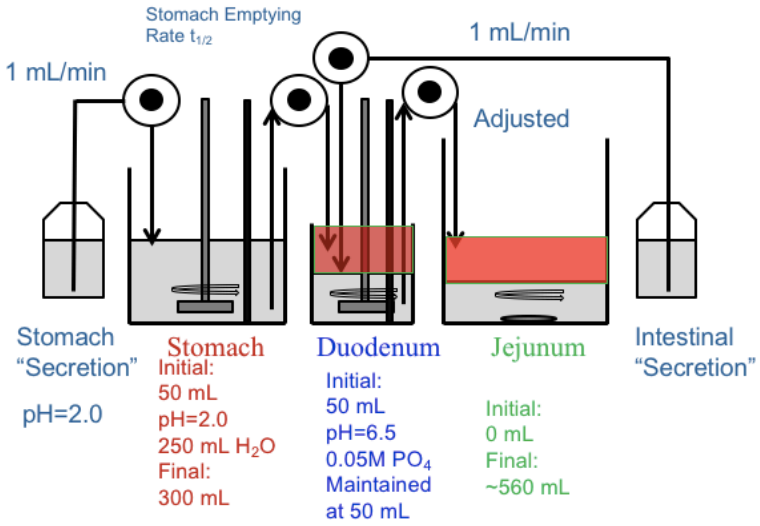
$$Sh = 1 + \Delta_{confinement} + \Delta_{shear}$$

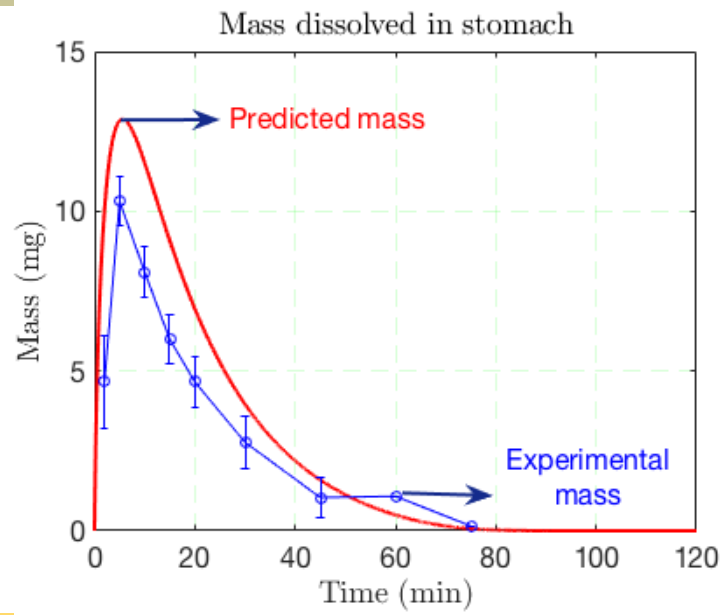
Prediction vs. Experiments for Non-Disintegrated Tablet (800 mg Ibuprofen)

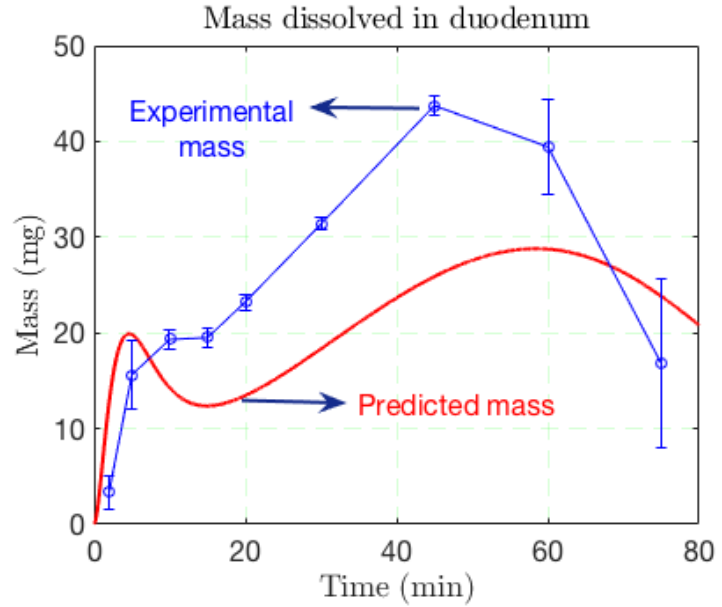


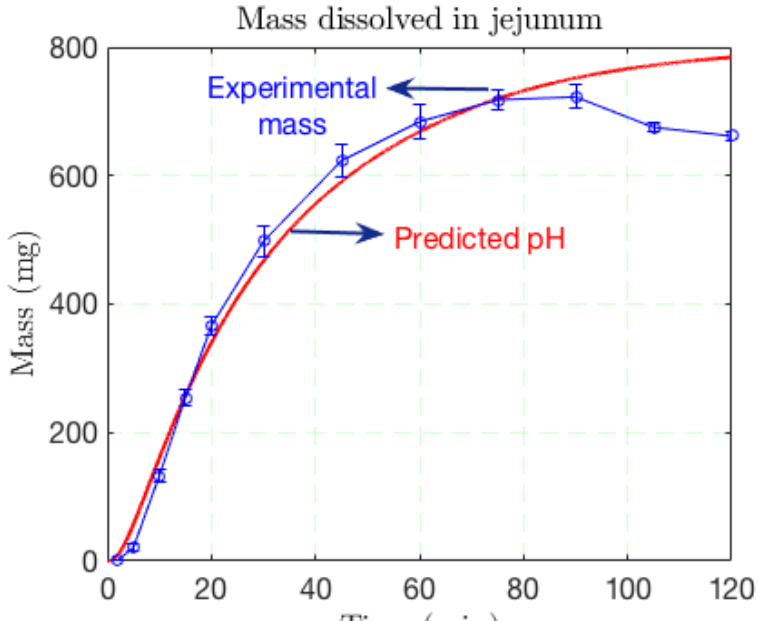


$t_{1/2} = 13\ min$









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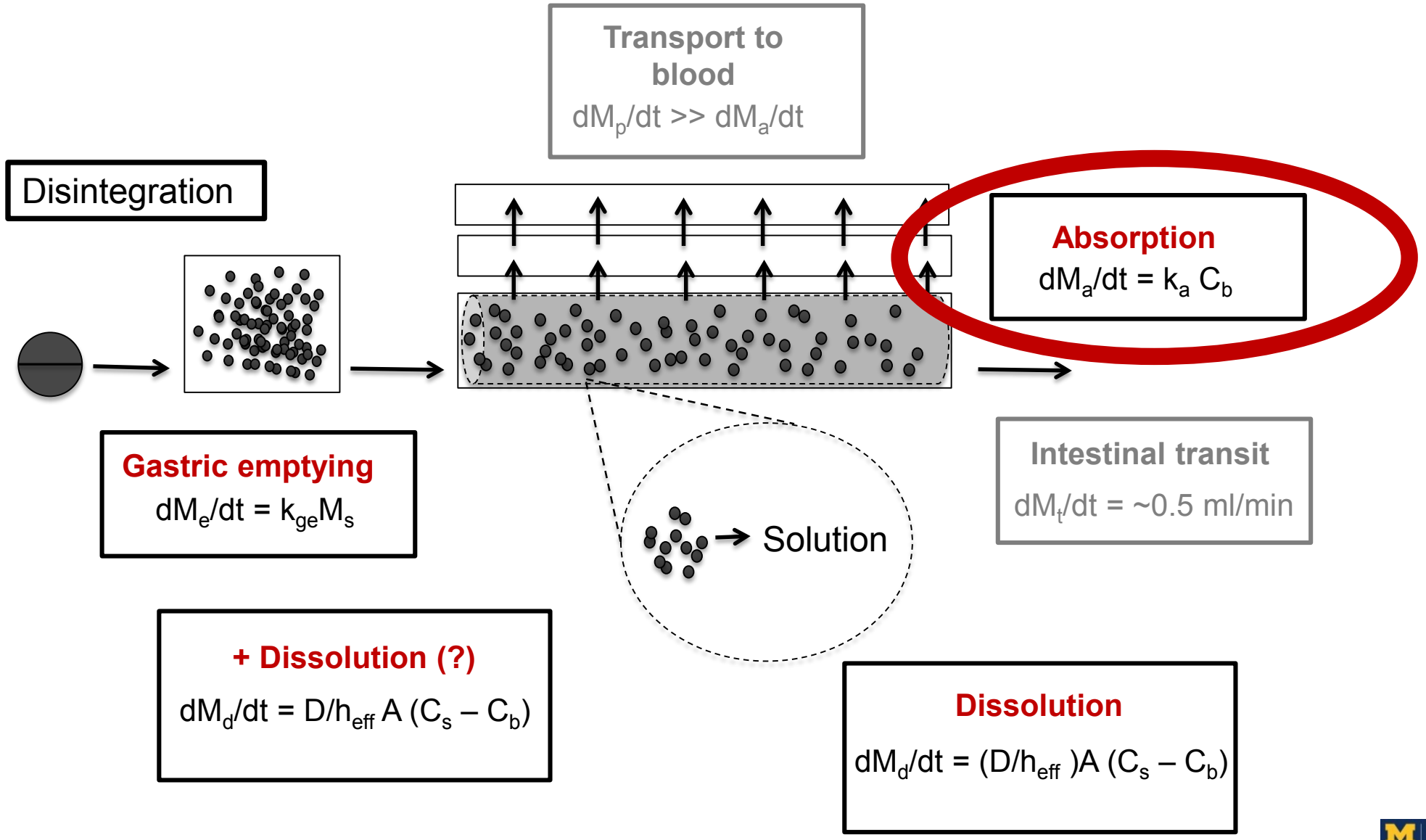
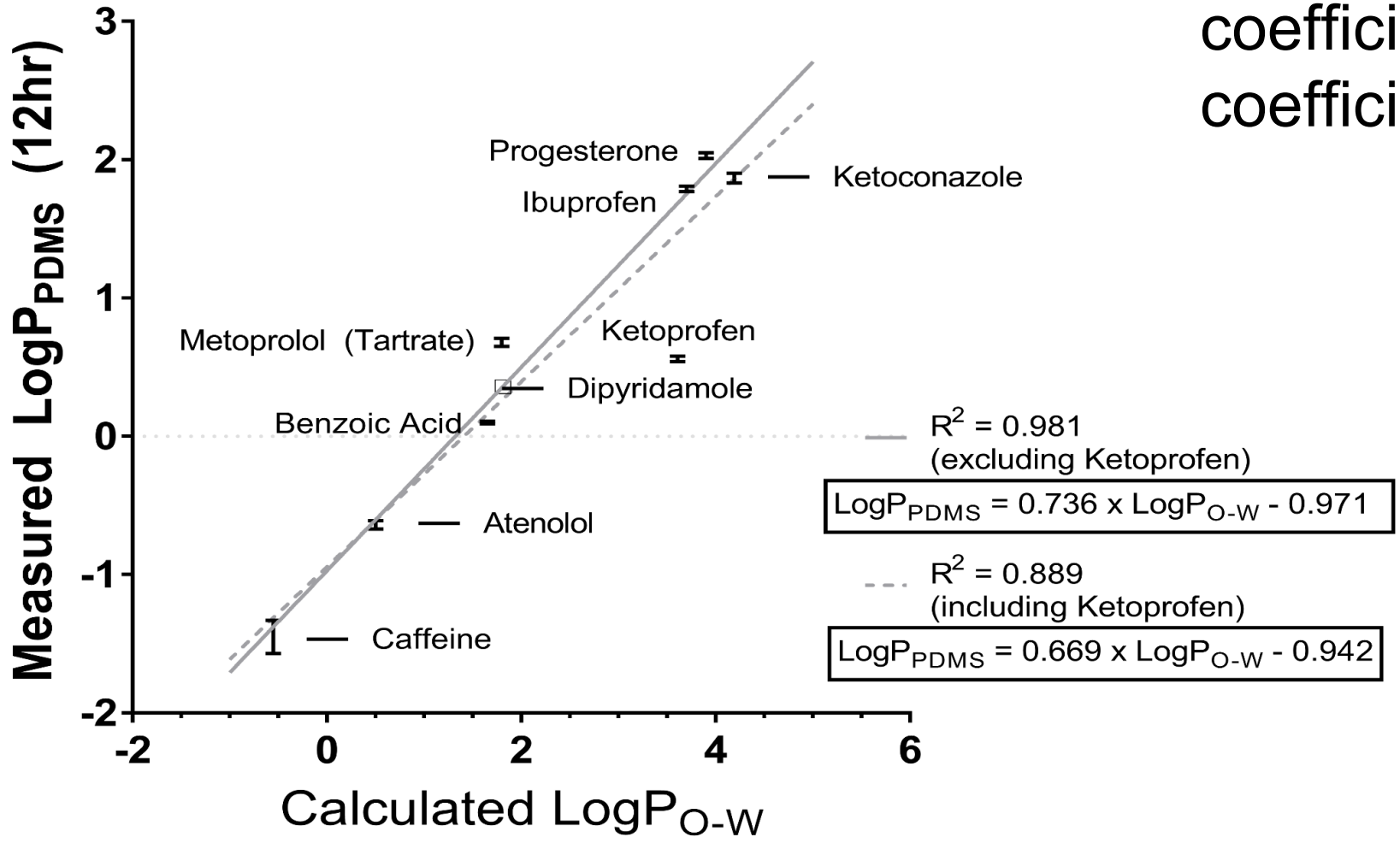
Goal: Integrate physical chemistry and physiology into a dissolution system that is kinetically relevant



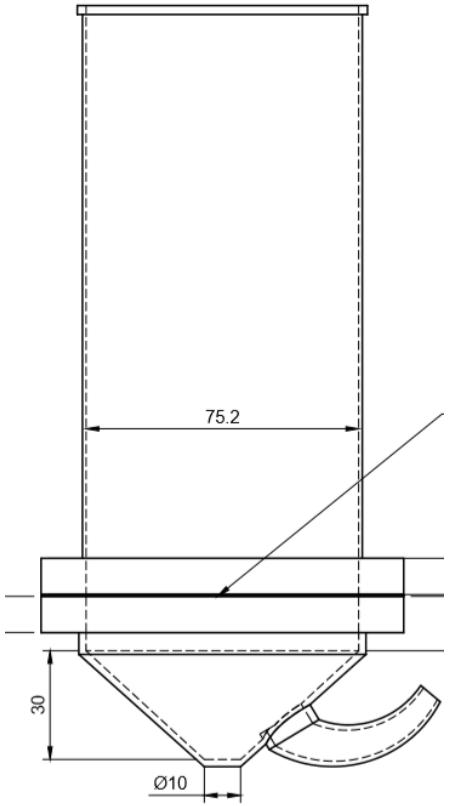
Simulating Absorption: Polydimethyl siloxane (PDMS) Membrane to simulate Absorption:

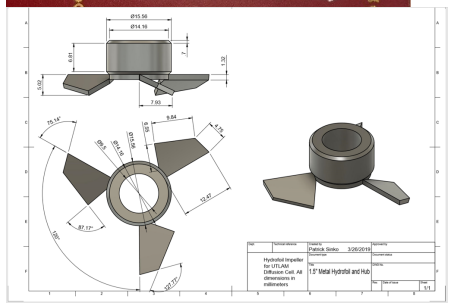
- Structure based prediction yields PDMS partition coefficients and diffusion coefficients



Ultra Thin Large Area Membrane (UTLAM) Diffusion Cell

Spin-Cast PDMS Membrane, Laser Cut Stainless Steel membrane support



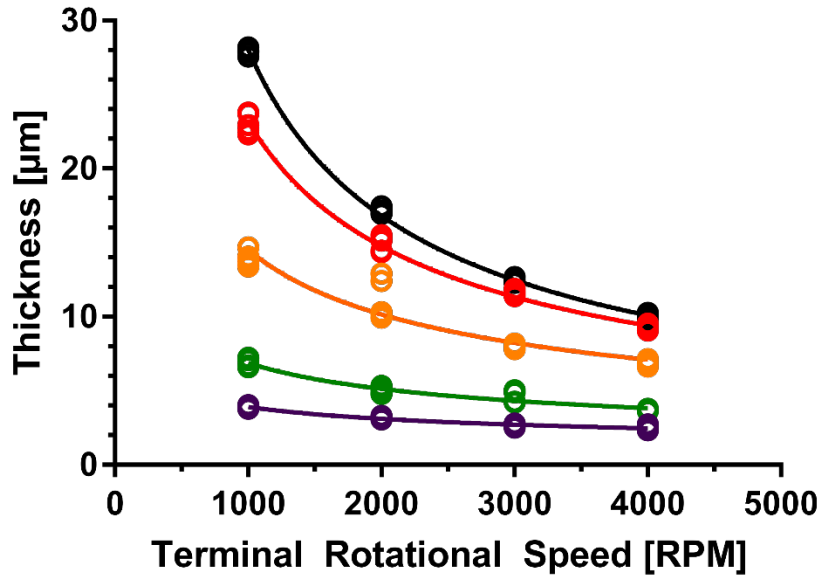


PDMS Membranes prepared using Spin-casting method

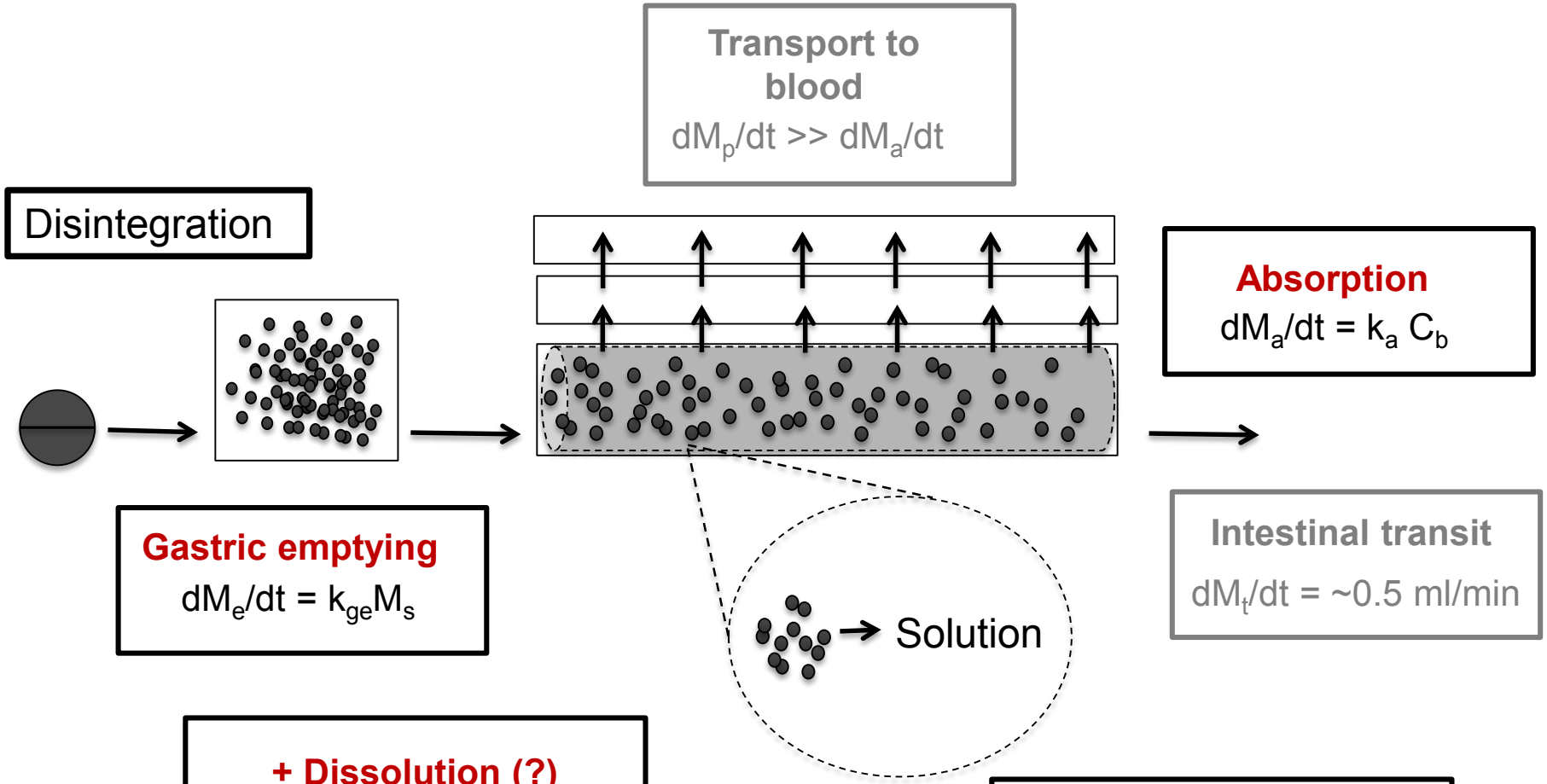
Spin Art

Membrane Thickness ~12 μm

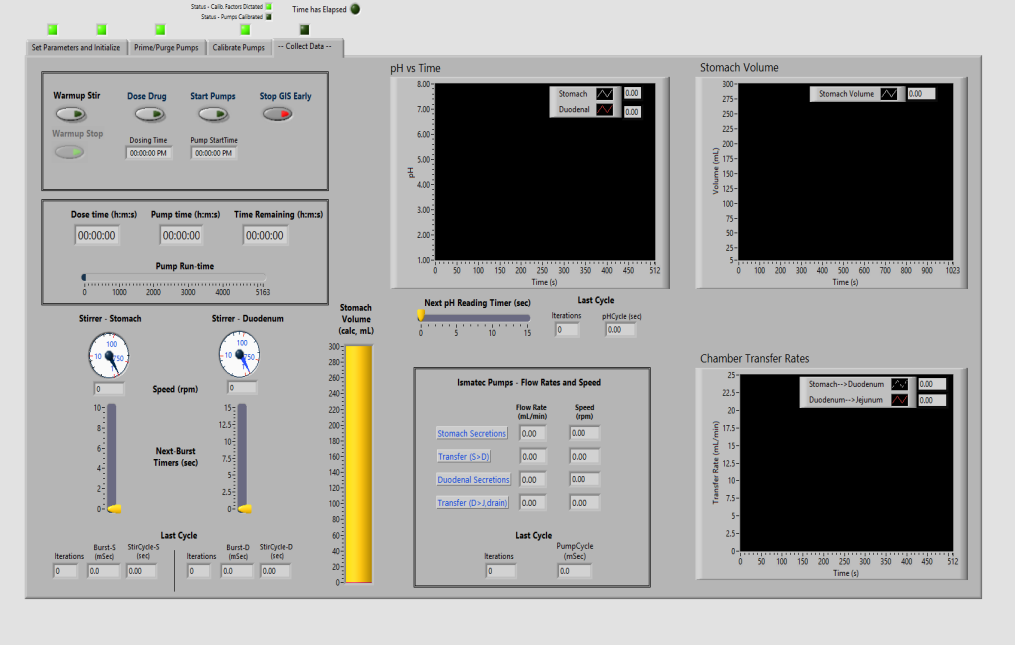
Membrane Effective Area ~ 22 cm^2

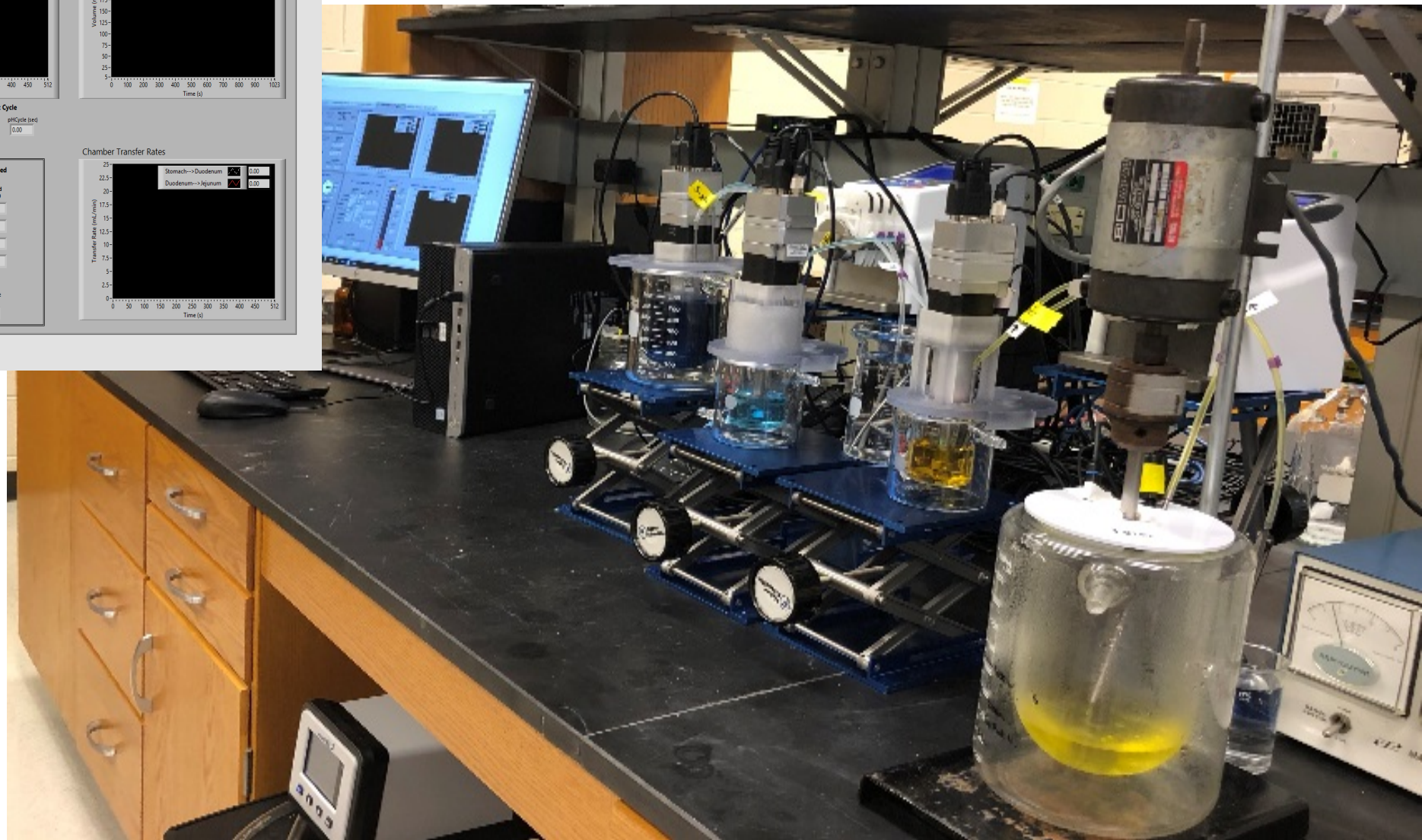


Goal: Integrate physical chemistry and physiology into a dissolution system that is kinetically relevant



GIS Device


Set Parameters and Initialize
Prime/Purge Pumps
Calibrate Pumps
-- Collect Data --
Warmup Stir
Dose Drug
Start Pumps
Stop GIS Early
Warmup Stop
Dosing Time
Pump StartTime
Dose time (h:m:s)
Pump time (h:m:s)
Time Remaining (h:m:s)
Pump Run-time
Stirrer - Stomach
Stirrer - Duodenum
Speed (rpm)
Next Burst Timers (sec)
Last Cycle
Stomach Volume (calc, mL)
pH vs Time
Stomach
Duodenal
Next pH Reading Timer (sec)
Last Cycle
Ismatec Pumps - Flow Rates and Speed
Flow Rate (mL/min)
Speed (rpm)
Stomach Secretions
Transfer (S>D)
Duodenal Secretions
Transfer (D>),drain)
Last Cycle
PumpCycle (mSec)
Stomach Volume
Chamber Transfer Rates
Stomach-->Duodenum
Duodenum-->Jejunum
Transfer Rate (mL/min)
Time (s)



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Dissolution Testing: The Future

Need to transition to multiple dissolution methodologies for different purposes

- Quality control (eg: Good, Fast, and Cheap, for change control)
- In Vivo Predictive (eg: not necessarily Fast or Cheap, for QbD purposes)

In vivo Predictive Dissolution (IPD) should:

- Be physiologically relevant
- Consider drug properties: (acid, base, neutral)
- Utilize appropriate dissolution methodology from several options (no less, no more)
  - Current compendial methods (eg: Apparatus 1, 2, 3, 4)
  - Multicompartment systems: Gastrointestinal Simulators (eg: ASD, GIS, TIM)
  - Multiphase systems to simulate absorption: (eg: Biphasic, polymer membrane systems)
  - pH – Dilution methods
  - Other?

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- Niloufar Salehi — Graduate Student
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- Sarah Harris — Undergraduate BSPS student
- Yue Yuan — Undergraduate BSPS student
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- Susumu Takeuchi, PhD — Visiting Scientist
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Questions, Comments, Discussion?