New Scientific Directions in Oral Bioequivalence(BE):

Formulation Predictive Dissolution-*In Vivo* Predictive Dissolution

[Implications for Product Development and QC Standards (QbD, PAT, SUPAC, BE)]

Charles R Walgreen, Jr. Professor

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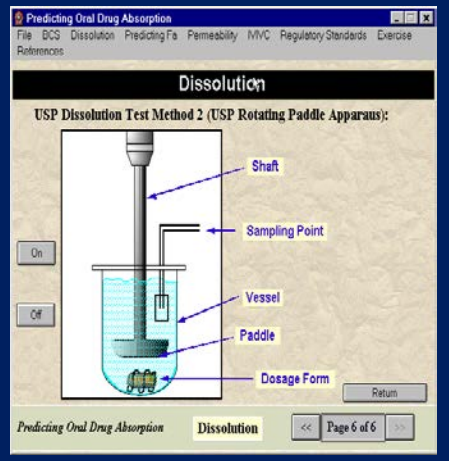
2010

1950

1970



OrBiTo June 27-29, 2017 : Finland

New Era in Mechanistic BE Science: Multidisciplinary

- Gastroenterologists (William Hasler, MD)
  - Catheterization, motility
- Statistical Analysis (Kerby Shedden, PhD)
  - Signal Analysis
- Chemical Engineers (Robert Ziff, PhD)
- Fluid Dynamics (James Brasseur, PhD)
- MRI Fluid (Luca Marciaini, PhD))
- Pharmaceutical Scientists (Gordon Amidon, PhD, Greg Amidon, PhD, Duxin Sun, PhD)

Project Personnel

- Pharm. Sci.
- Statistics
- Chem. Eng.
- CFD
- Physics (MRI)

*UNIVERSITY OF MICHIGAN

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Gregory Amidon, Ph.D. Co-I
Duxin Sun, Ph.D.
Yasuhiro Tsume, Asst. Research Scientist
Paulo Paixao, Visiting Scientist
Marival Bermejo, Visiting Scientist
Bart Hens, PostDoc
Raimar Loebenberg, Visiting Scientist
Jozef Al-Gousous, PostDoc
Arjang Talattof, Consultant
Nicholas Job, Grad Student
Patrick Sinko, Grad Student
Gail Benninghoff, Program Manager

Statistics
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Grants Management
Victoria Devulder, Grants Management

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Farhad Behafarid, Ph.D.

UNIVERSITY OF NOTTINGHAM (MRI)
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Nichola Abrehart, Research Assistant
Khaled Heissam, (PostDoc)

FDA

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Liang Zhao, DQMM Division Director
Robert Lionberger, ORS Office Director
Minori Kinjo, ORS RIHSC PM
Zongming Gao, Chemist
John Duan – Pharmacologist
Hong Wen - Chemist
Dajun Sun – DQMM/ORS/OGD/CDER
Stephanie Choi – Acting Associate Director for Science
Monifa Coleman, Team Lead, Contracting Officer
Ronald Rouse, CO, Division Director

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Dr. Peter Langguth (JGU Mainz, DE)
Dr. Hans Lennernäs (Uppsala, SE)
* Deceased

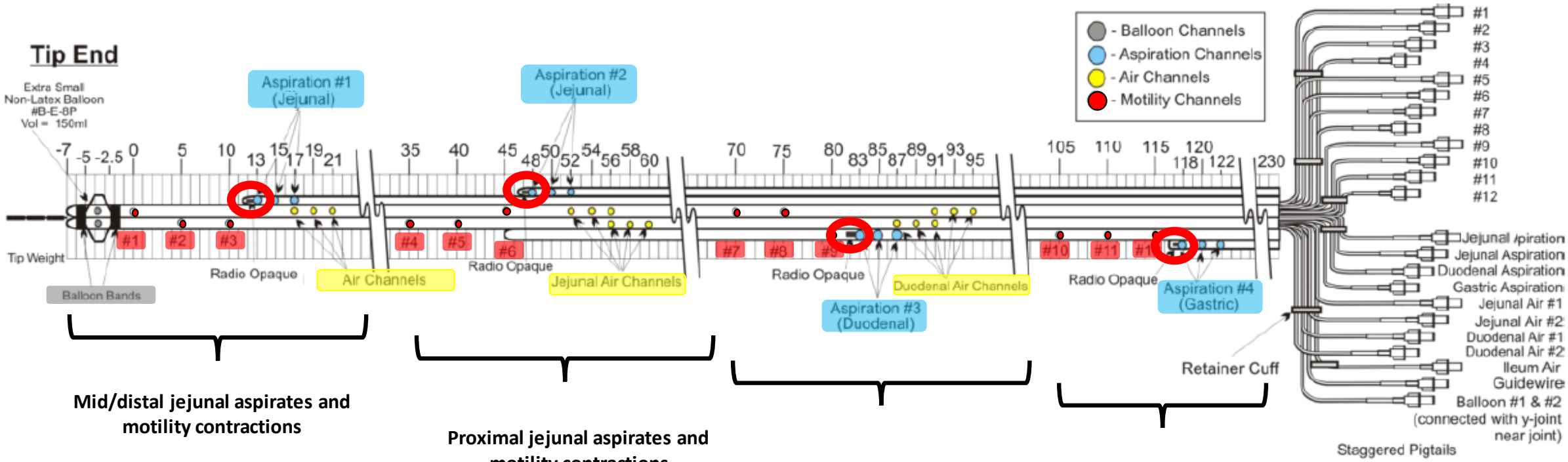
COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN

*Funding: FDA
HHSF223201510157C
HHSF223201310144C

FDA Project Goal

- Set a New mechanistic based method/test for bioequivalence (BE) evaluation of oral products
- Determine significant Gastrointestinal variables under BE protocol
- Develop *in vitro* test/method to compare products including statistical methods
- Develop a Formulation Predictive Dissolution Test Method

Customized 24 Channel Aspiration Catheter



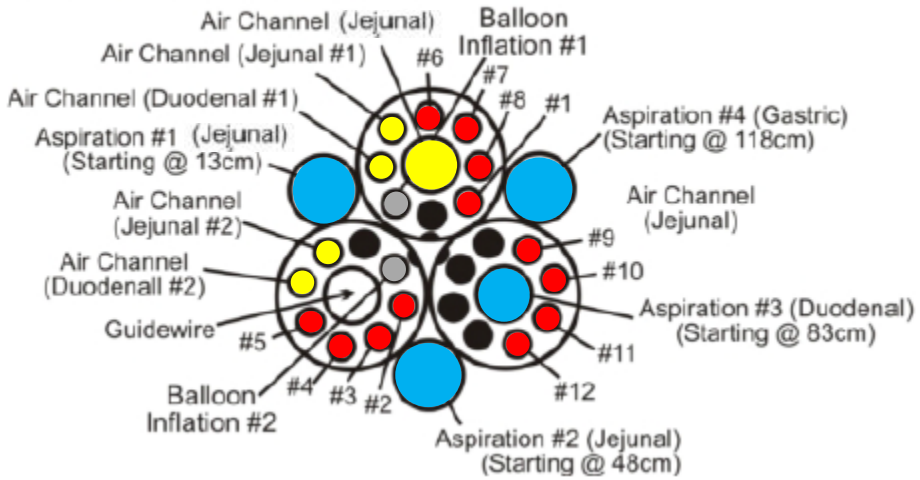
Mid/distal jejunal aspirates and motility contractions

Proximal jejunal aspirates and motility contractions

Duodenal aspirates and motility contractions

Gastric aspirates and motility contractions

Catheter Cross Section View

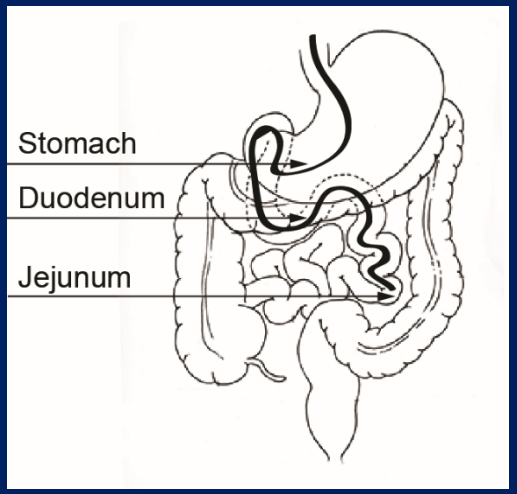


Before these markers, we have the aspiration channels

Study Enrollment

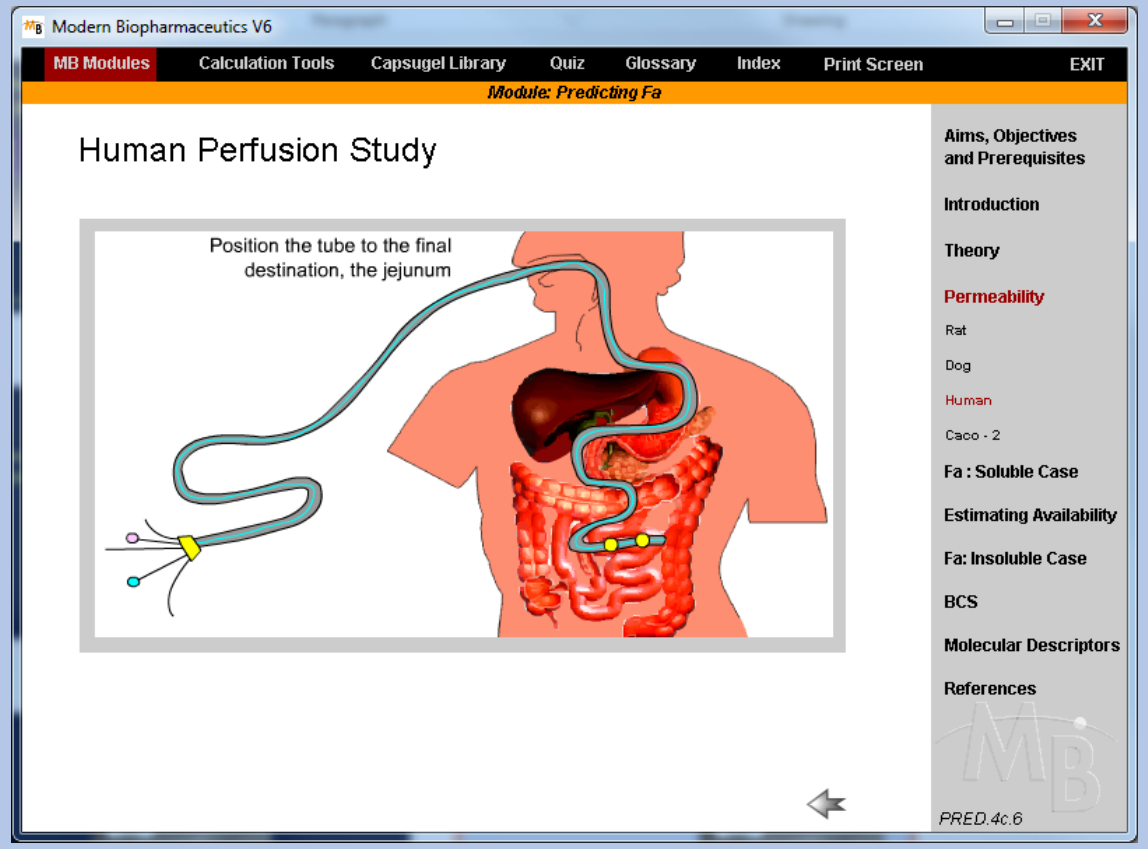
From 14JAN2015 to 20JUL2016

- 43 tube placement procedures performed
- 37 study visits with complete data collection
  - ~63% success rate
- 25 subjects; 12 with two visits for intrasubject variability estimation
- 20 fasted; 17 fed conditions
- Female (61%), male (39%)
- average age 30 years.
- Median weight of 79 kg (min 52 max 123)
- Body mass index of 25.7 [19.4, 37.7] kg/m2

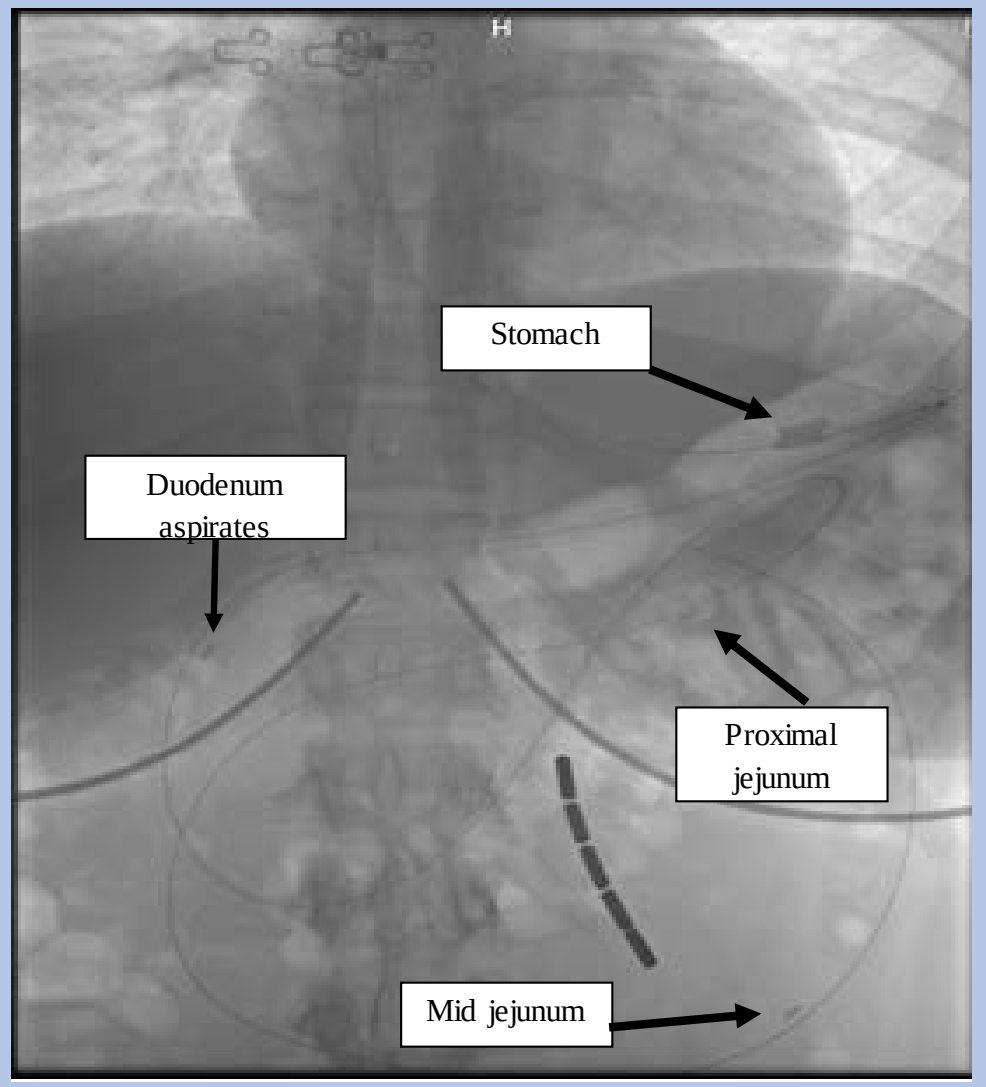


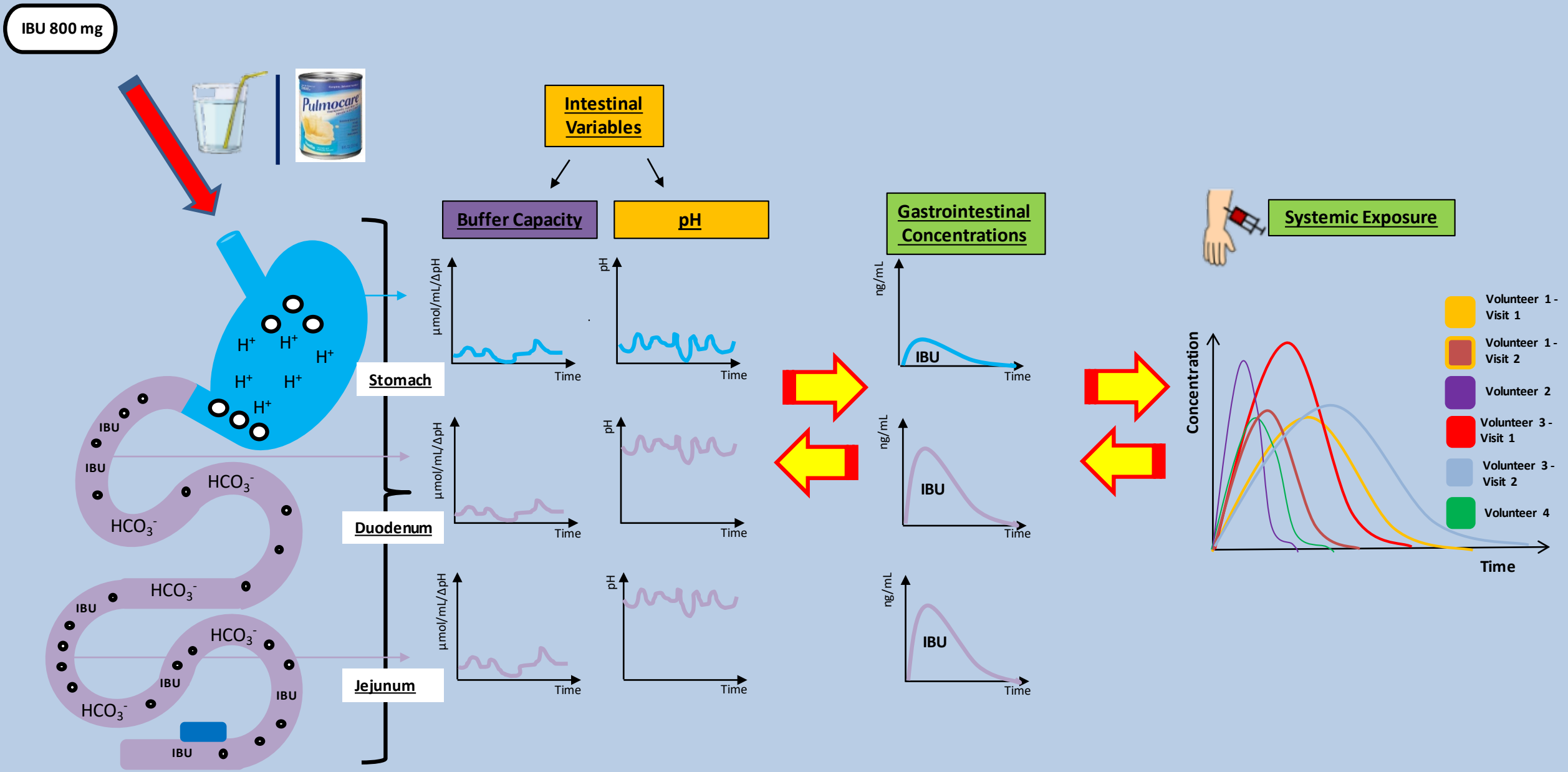
Measuring GI Variables

Tube Placement

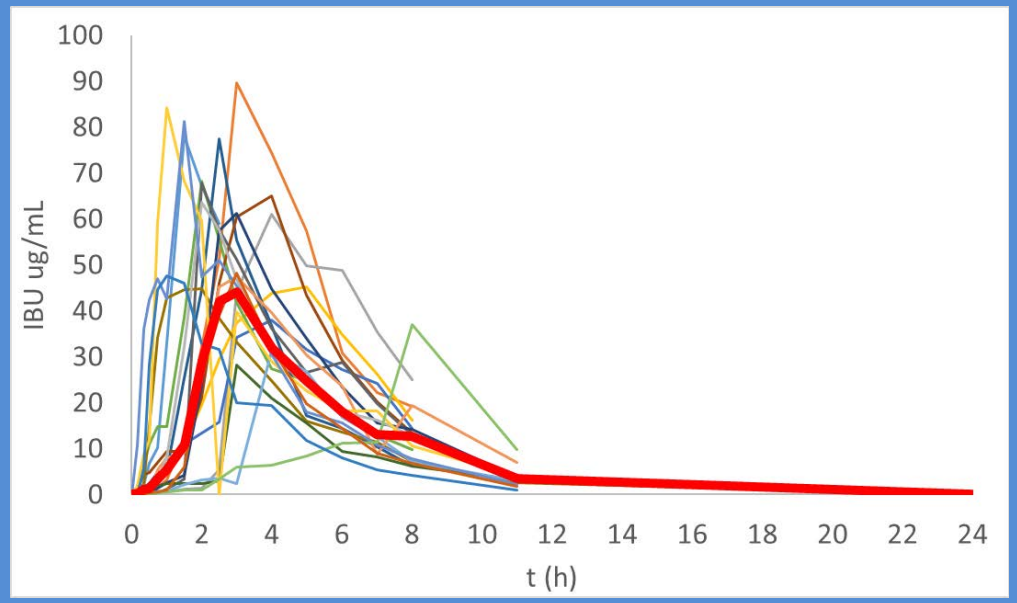


Fluoroscopy




IBU 800 mg
Pulmocare
Intestinal Variables
Buffer Capacity
pH
Gastrointestinal Concentrations
Systemic Exposure
Stomach
Duodenum
Jejunum
H+
IBU
HCO3-
µmol/mL/ΔpH
pH
ng/mL
Time
Concentration
Volunteer 1 - Visit 1
Volunteer 1 - Visit 2
Volunteer 2
Volunteer 3 - Visit 1
Volunteer 3 - Visit 2
Volunteer 4

Plasma Ibuprofen (Fasted: n = 20)

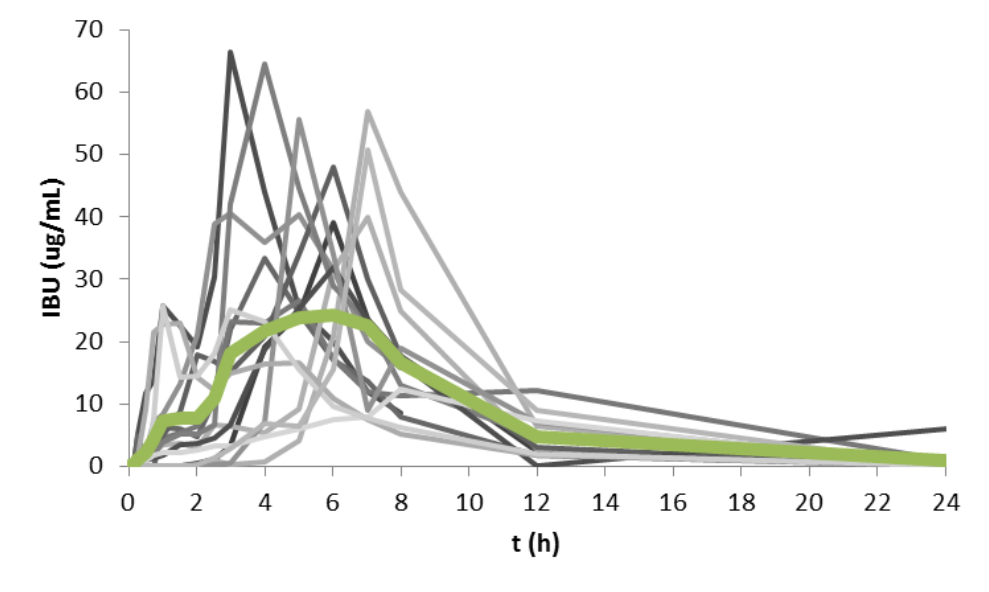


	Cmax		Tmax		AUC0-t	
	FASTED	FED	FASTED	FED	FASTED	FED
GeoMean	54	38	-	-	257	198
Mean	57	41	-	-	274	208
SD	18	16	-	-	95	65
CV	32	39	-	-	35	31
Median	-	-	3	5	-	-
Range	-	-	1 - 8	1 - 8	-	-
Fed/Fasted	0.69		1.67		0.77	

	Cmax*		Tmax		AUC*	
	fasted	fed	fasted	fed	fasted	fed
Geisslinger 1989	68	60	0.89	1.55	275	225
Kapil 2004	68	58	1.80	2.10	246	234
Klueglich 2005	68	52	1.40	1.60	234	184
Tanner 2010	64	49	1.25	2.00	218	236
Levine 1992	84	64	1.30	1.60	268	233
Mean	70	57	1.33	1.77	248	223
Fed/Fasted	0.81		1.33		0.90	
* - values adjusted to 800 mg						

Ibuprofen Dose 800 mg
Dosing volume 250 mL water with
Phenol Red as non-absorbable marker
(100µg/mL)

Plasma Ibuprofen (Fed: n = 15)



	Cmax		Tmax		AUC0-t	
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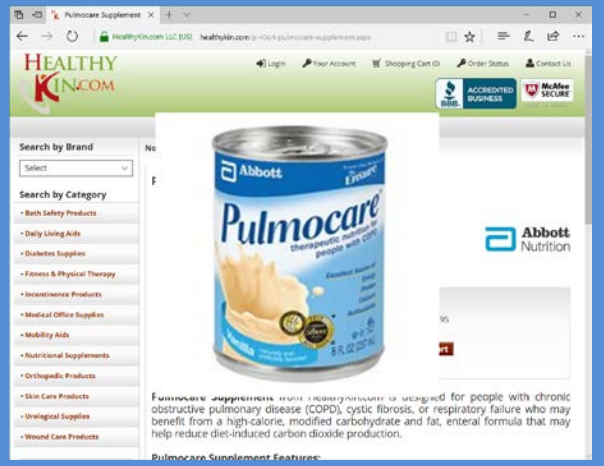
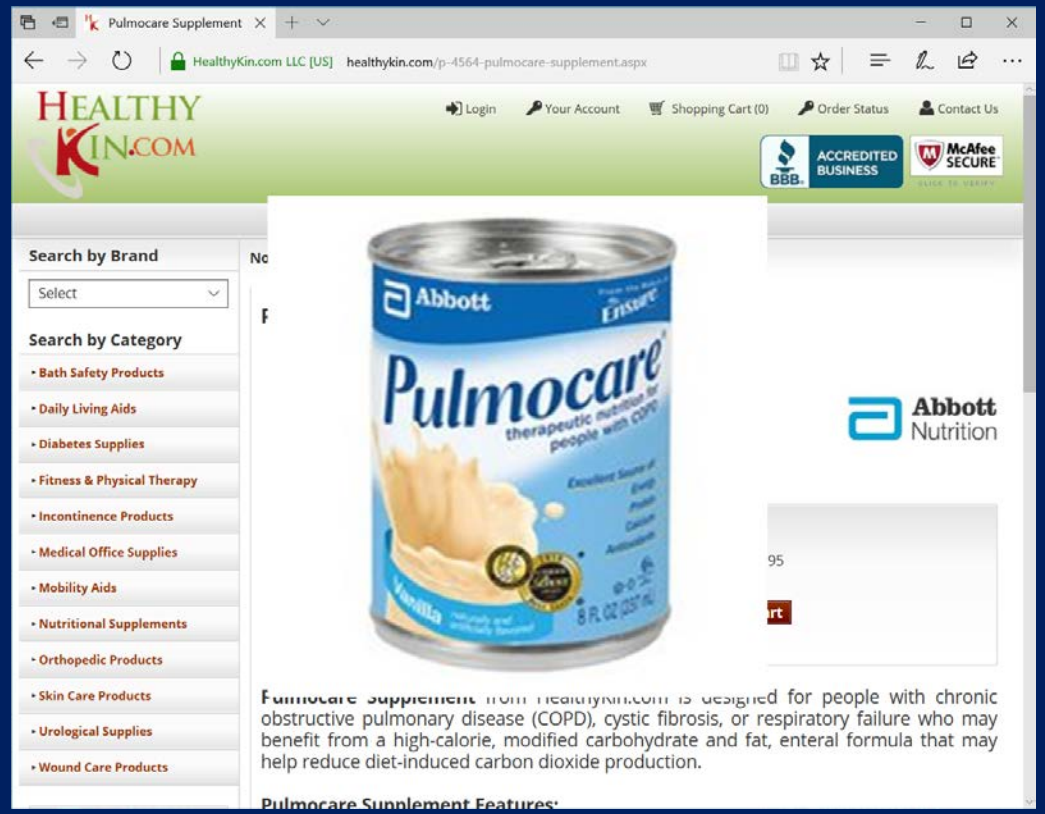
* - values adjusted to 800 mg						

Liquid Meal (~350 Cal)

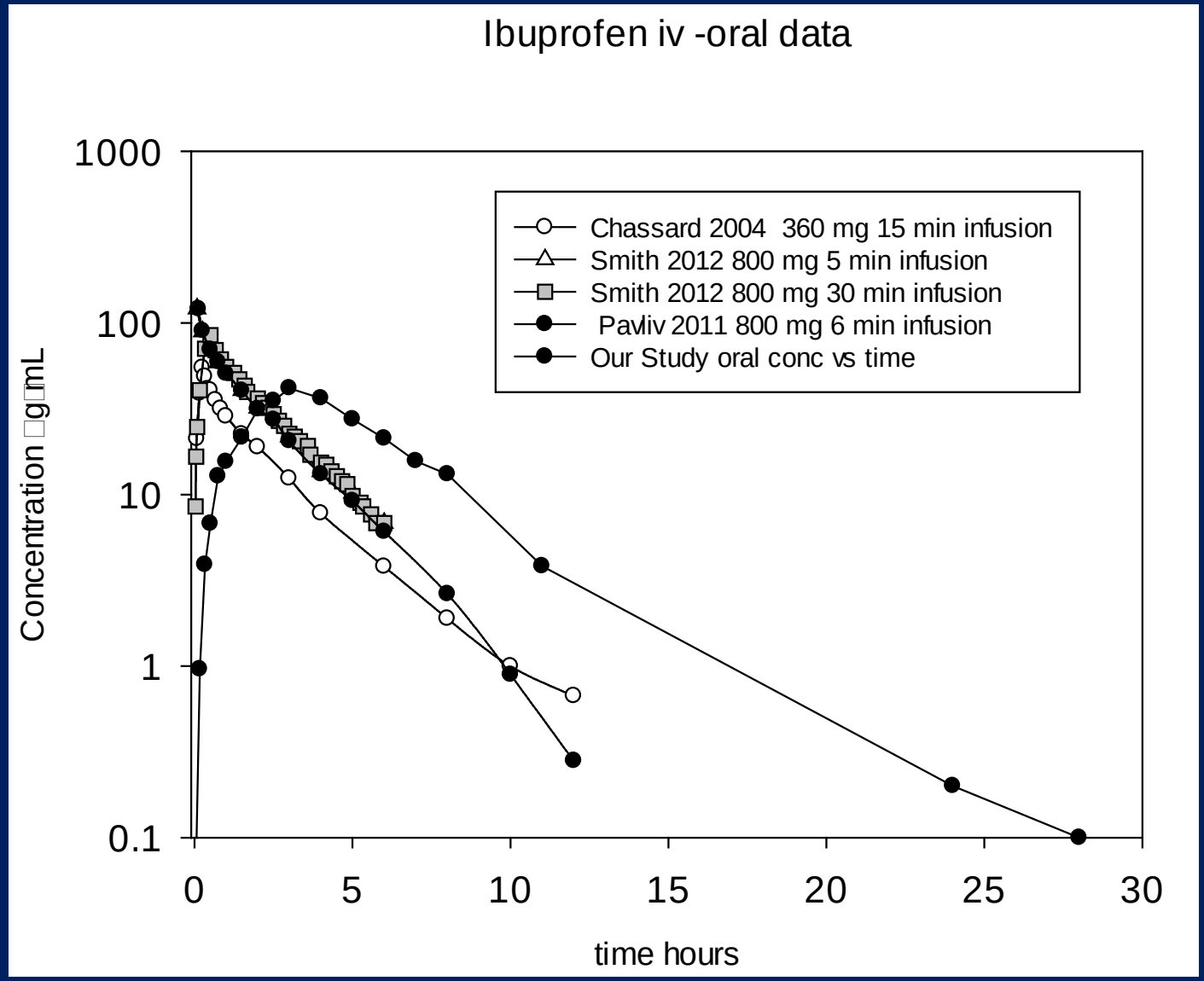


Pulmocare®

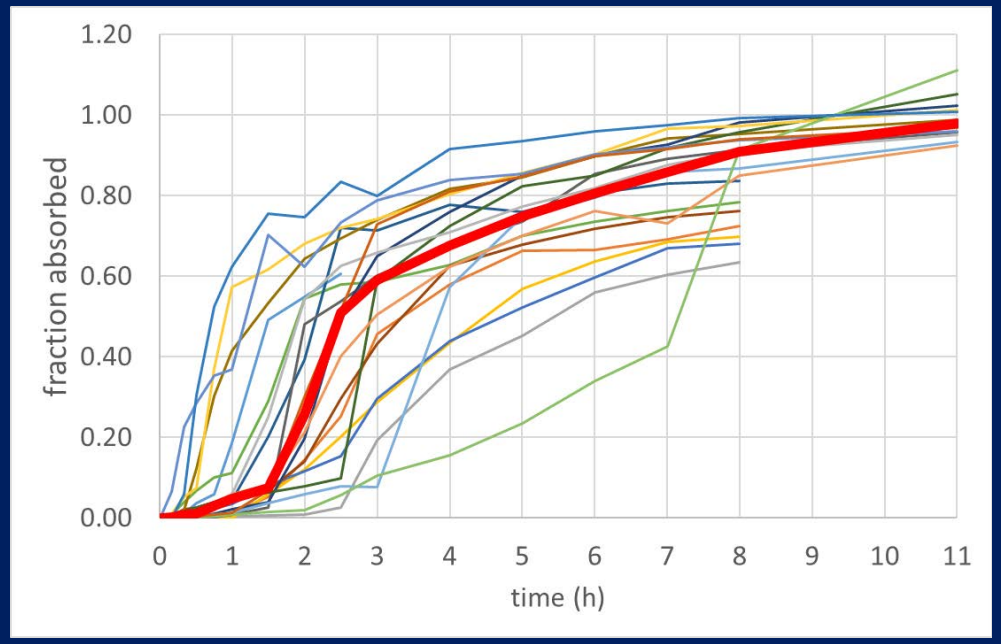


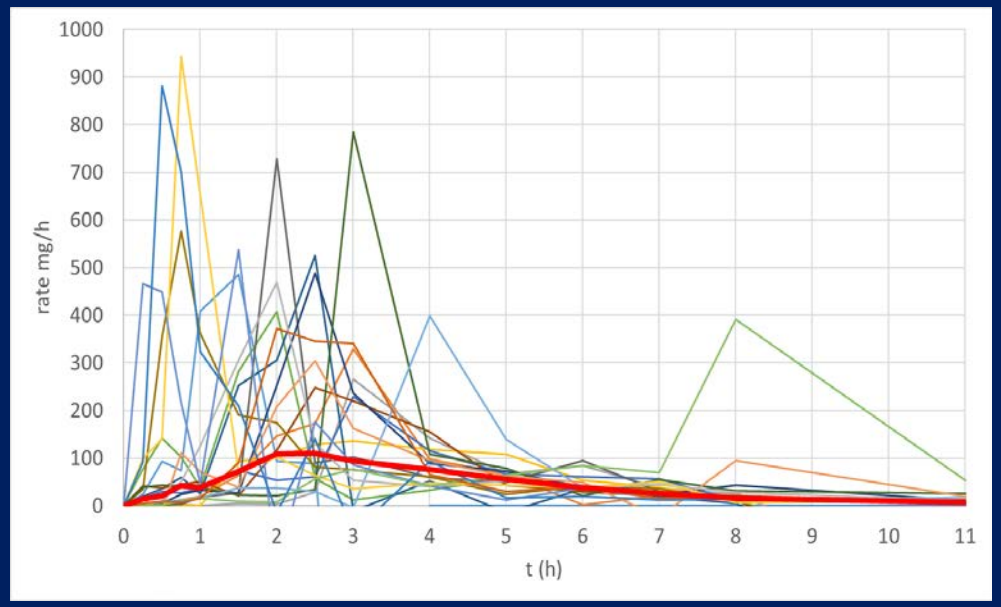
One can of Pulmocare®:
355 cal
237 mL/ 8FL OZ
pH 6.6
Buffer Capacity (µmol/mL/ΔpH): 3.33 ± 1.44
14.8 g protein
22.1 g fat
25.0 g carbohydrate
372 mL on average administered (**range: 7-474 mL**)
586 cal on average taken (**range: 10.5-711**)

IBU IV data from literature compared to our study



Deconvolution Fasted

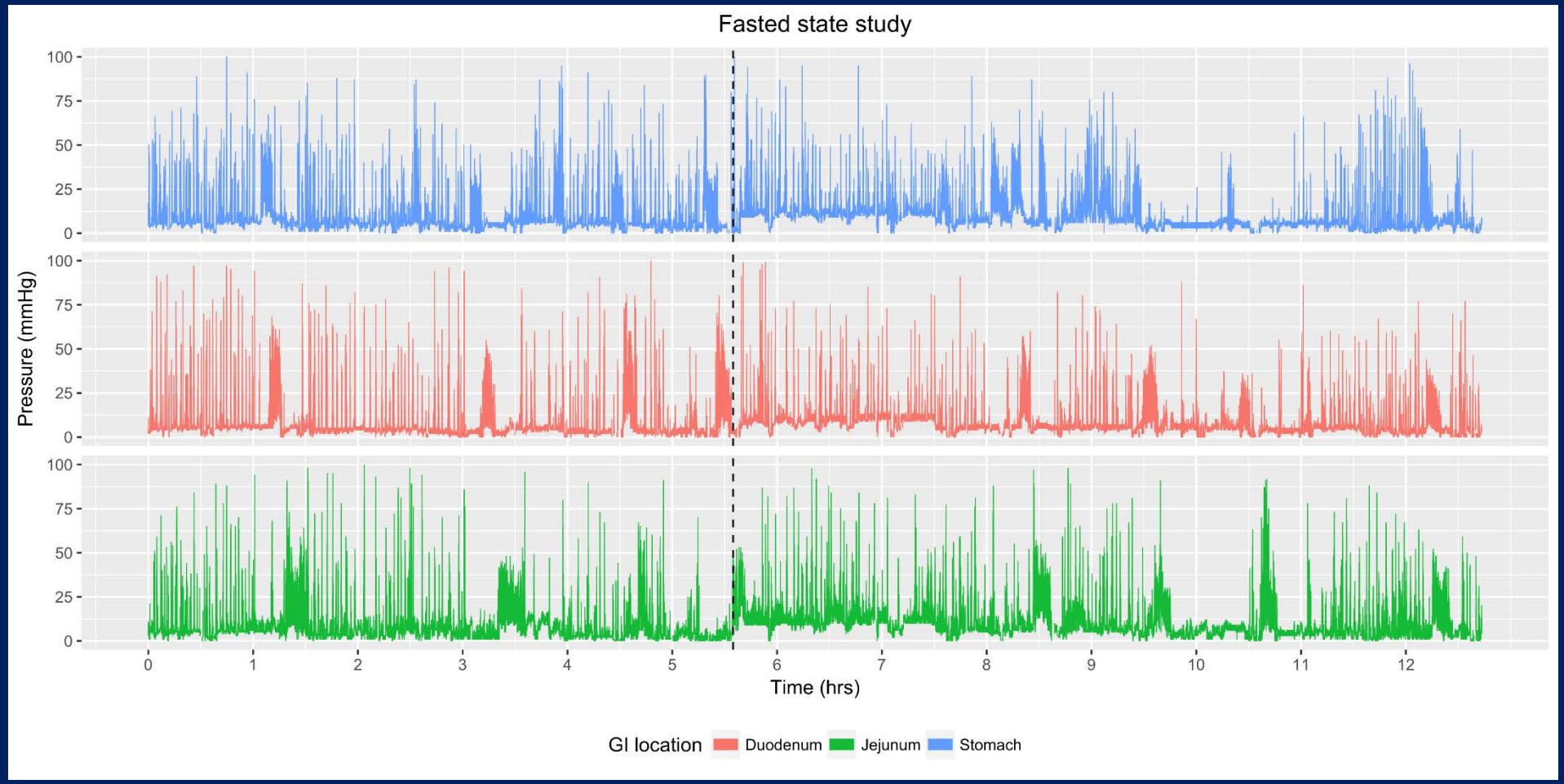




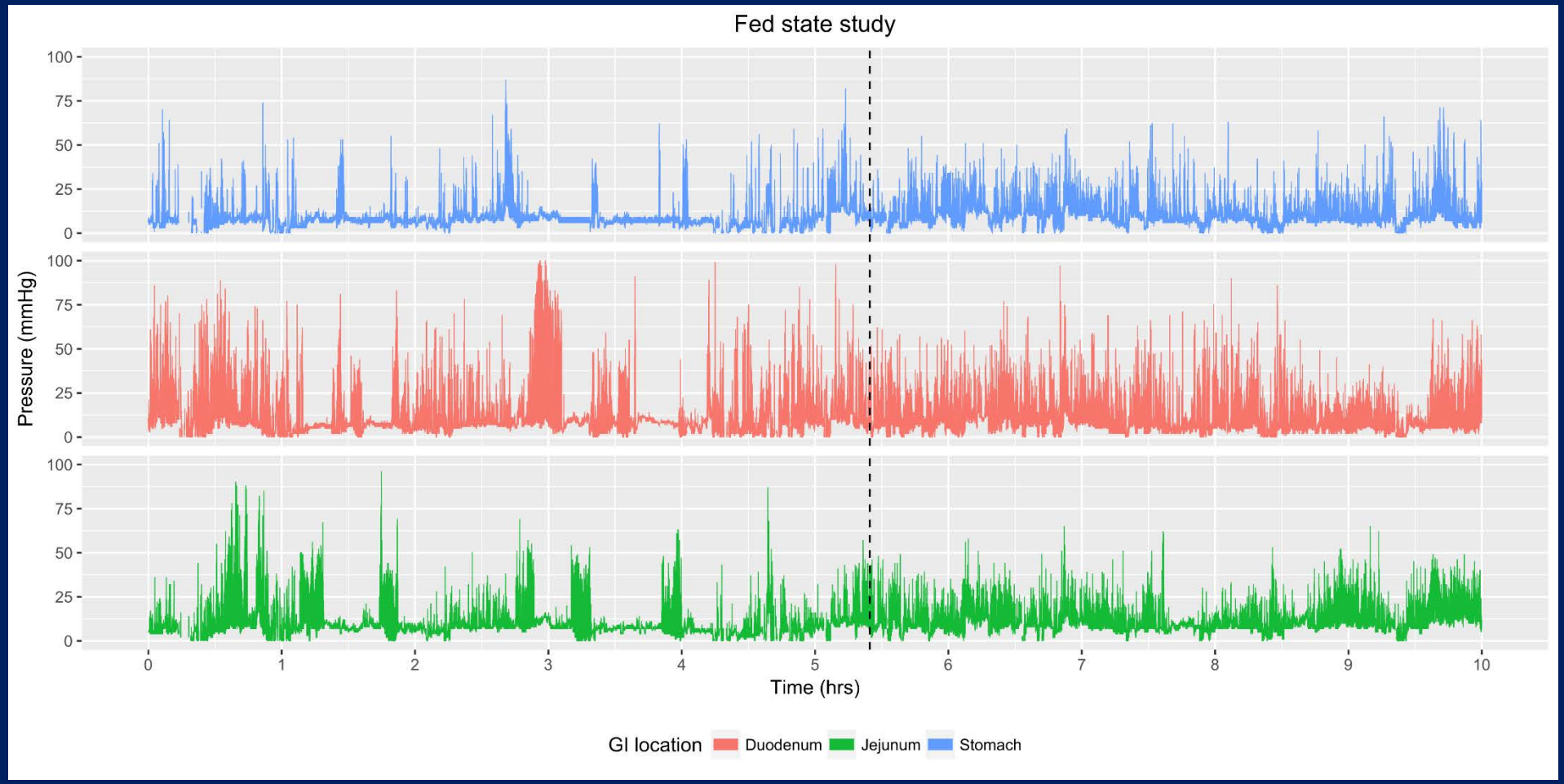
Subject	time to 50% fa (h)
B003V1	1.58
B004V1	3.35
B004V2	5.45
B005V1	4.49
B005V2	4.73
B006V1	1.92
B0017V1	2.16
B0017V2	3.35
B042V1	2.17
B042V2	1.36
B44V1	2.50
B049V1	2.91
B049V2	3.85
B052V1	2.98
B053V1	1.93
B055V1	0.91
B055V2	1.20
B063V1	8.43
B065V1	0.72
B065V2	2.46
average	2.92
median	2.48
max	8.43
min	0.72

Gastrointestinal Motility

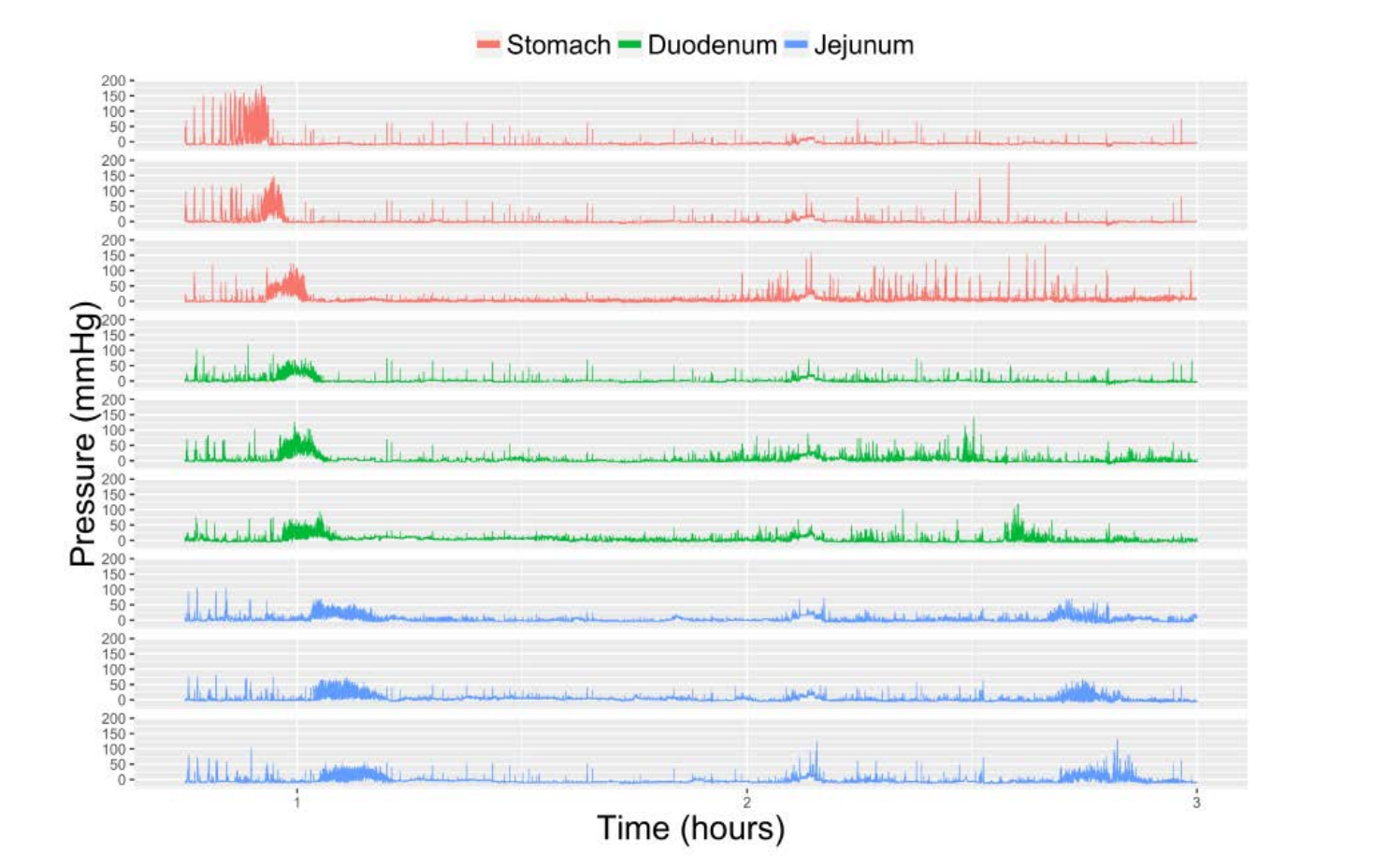
11 hr Fasted Motility Recording Plus Ibu Dose



11 hr Fed Motility Recording Plus Ibu Dose

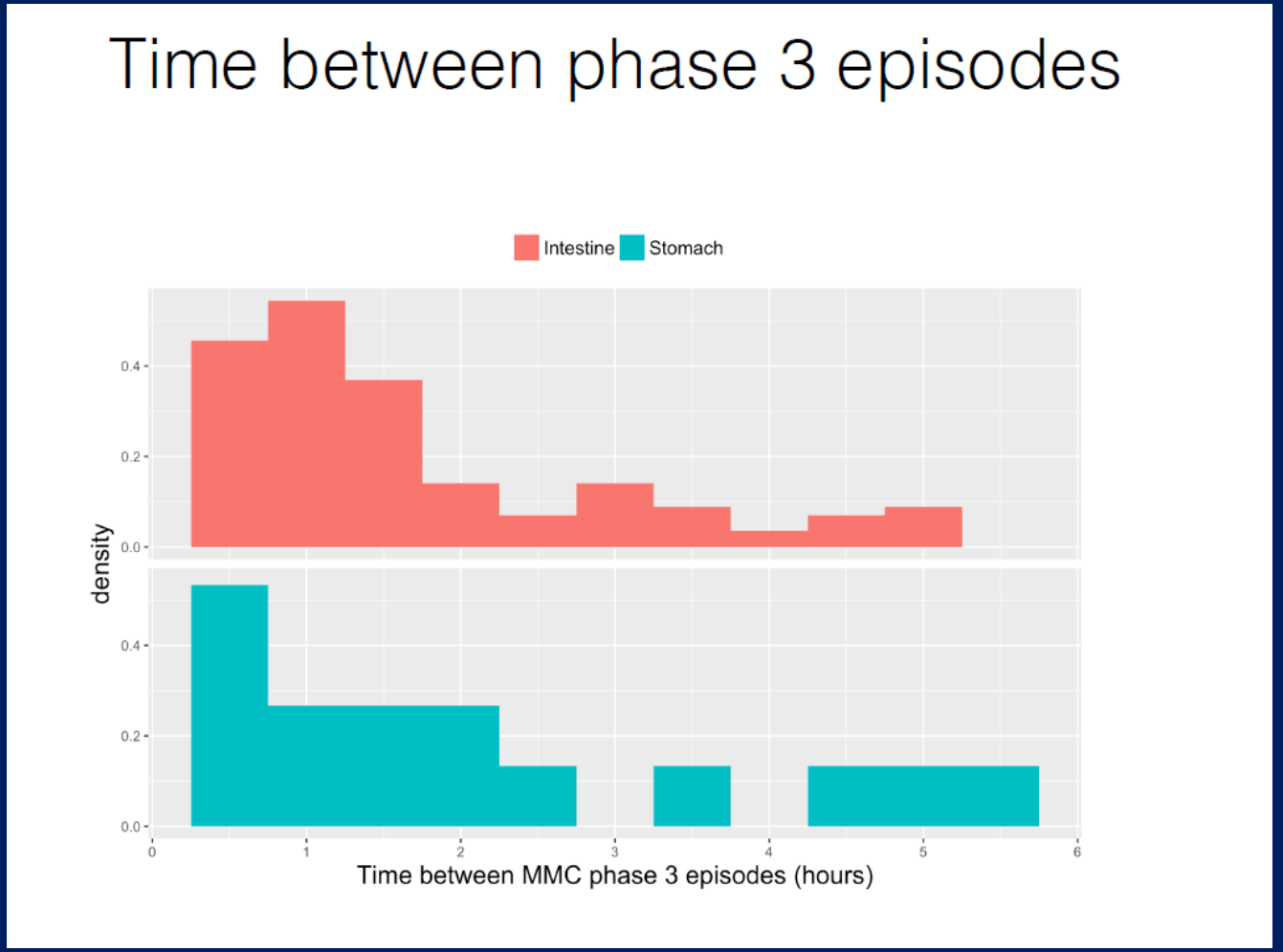


Gastrointestinal Motility Recordings (Fasted)



- Phase III (Fasted) are strongest intestinal contracts ([pressure)
- Phase III is cyclical and periodic
- Period ~2 hr.

Phase III Period Distribution



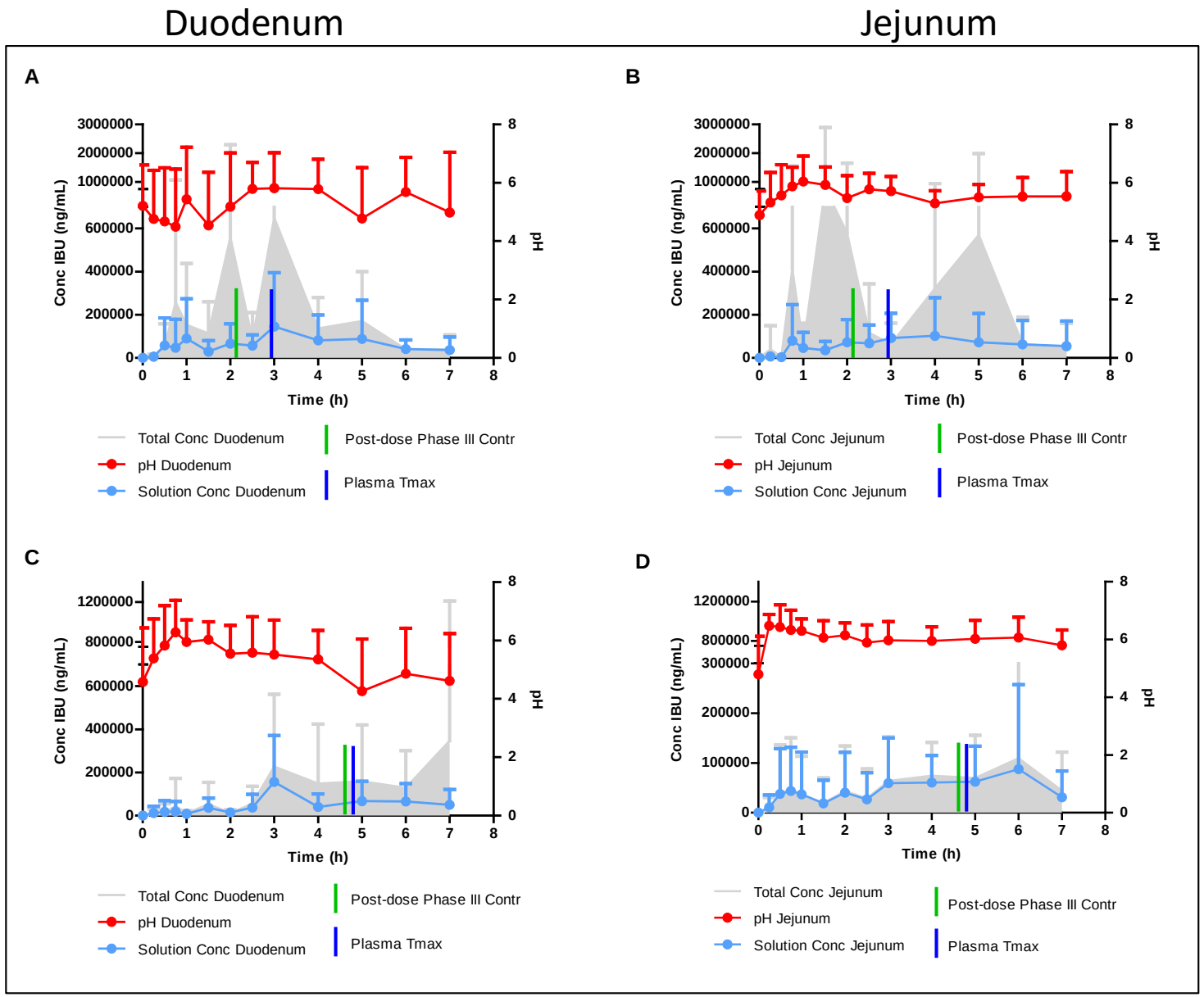
First Surprising Results

Ibuprofen in the GI Tract at 7 hrs

Measured Gastrointestinal pH & Ibuprofen Levels

Fasted (A,B)

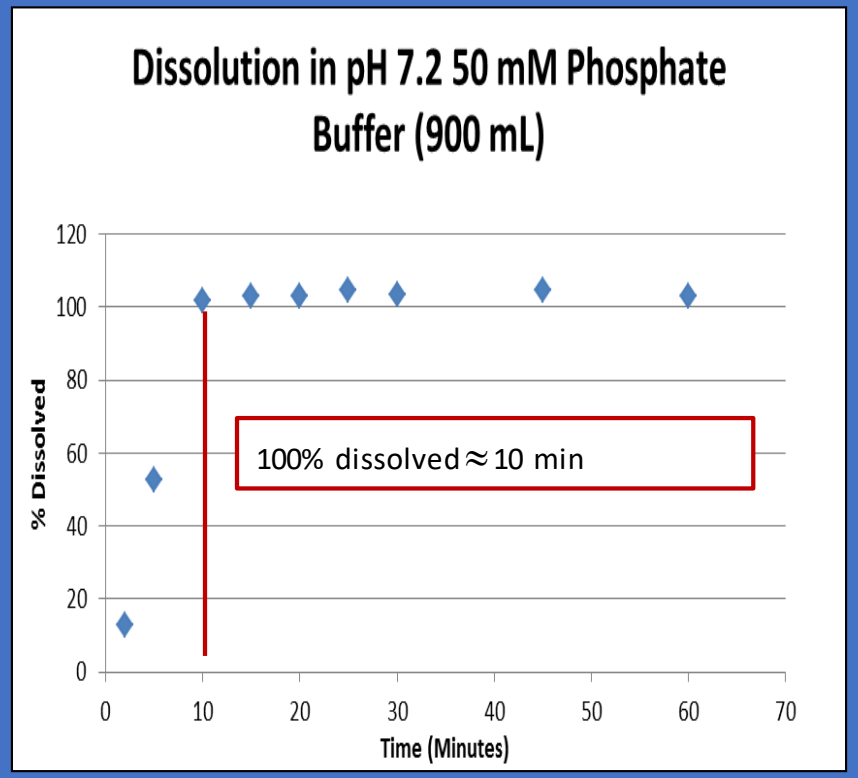
Fed(C,D)

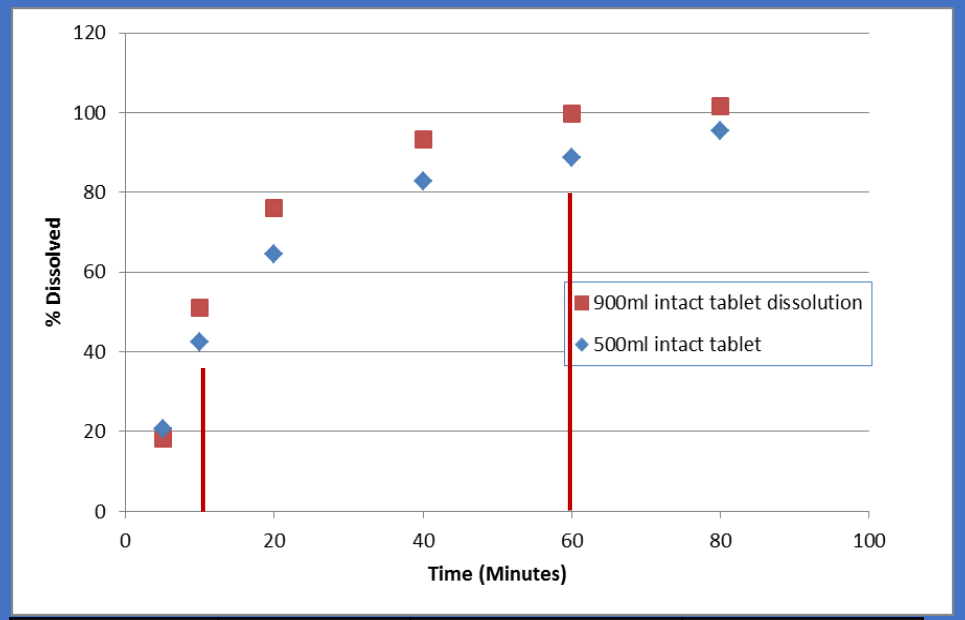


Dissolution of Clinical Dosage form

(800 mg Dr. Reddy's Reference Listed Drug(RLD))

800mg intact tablet dissolution in pH 6.5, 10 mM HCO_3 buffer (15% CO_2 & total buffer concentration of 14 mM). USP 2 apparatus, 50 rpm & 37 °C





Bulk Volume, ml	Extent of dissolution	Time to dissolve 50% dose, min	Time to 100%, min
500	105%	13	80
900	102%	10	60

USP Test: pH =7.2 50mM Phoshate
50 RPM paddle (Apparatus 2)
Not Less Than 80% dissolved in 60 min

Second Surprising Results

Buffer Capacity in GI Tract is Very Low

Low GI Buffer Capacity*

04/24/2017

Low Buffer Capacity Along The Human Gastrointestinal Tract: Implications for *in vivo* Dissolution and Absorption of Ionized Drugs

Bart Hens[1], Yasuhiro Tsume[1], Marival Bermejo[2], Joseph Dickens[3], Kerby Shedden[3], Niloufar Salehi[1], Bo Wen[1], Jeffrey Wysocki[1], Paulo Paixao[4], Raimar Loebenberg[5], Mark J. Koenigsknecht[1], Allen Lee[6], Jason R. Baker[6], William L. Hasler[6], Ann F. Fioritto[1], Greg Amidon[1], Alex Yu[1], Gail Benninghoff[7], Arjang Talattof[8], Robert Lionberger[8], Jianghong Fan[8], Duxin Sun[1], Gordon L. Amidon[1*]

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[3]Department of Statistics, University of Michigan 48109, Ann Arbor, USA

[4]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Professor Gama Pinto, 1649-003 Lisboa, Portugal

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[6]Department of Internal Medicine, College of Medicine, University of Michigan, Ann Arbor, Michigan 48109, United States

[7]Deloitte, Arlington, Virginia 22209, United States

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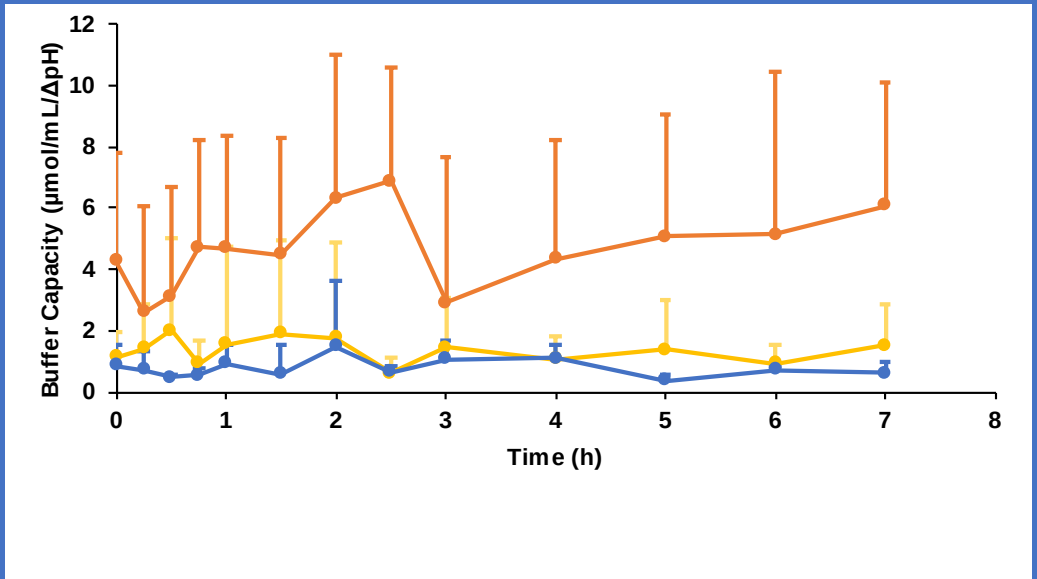
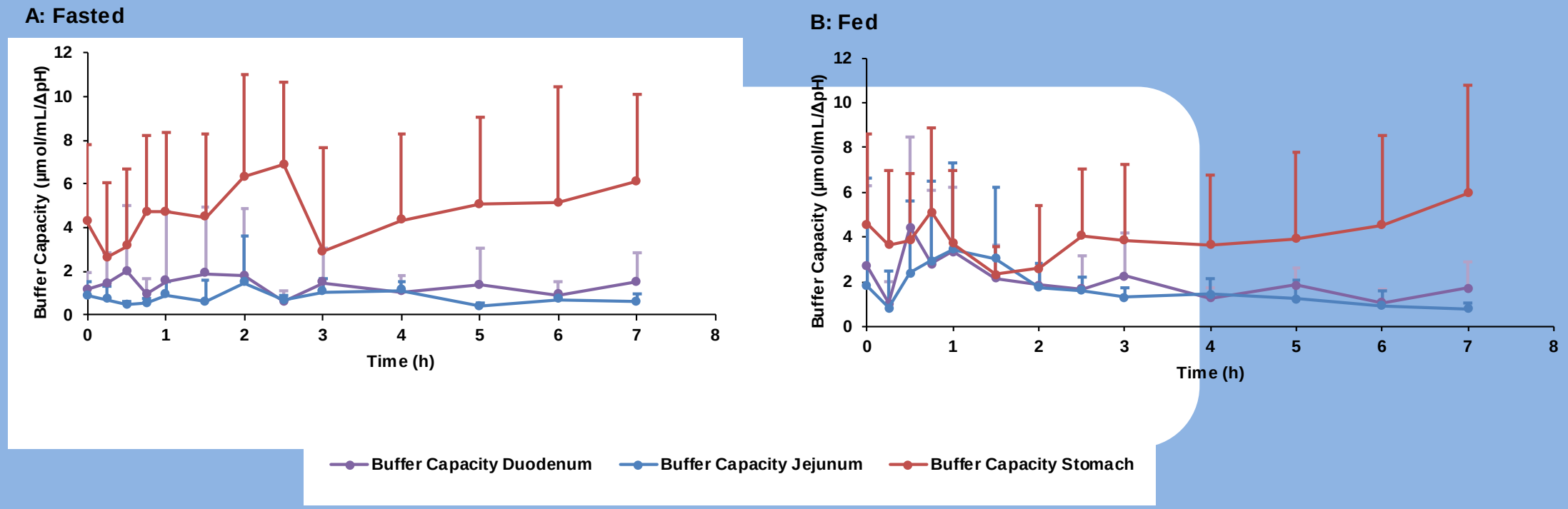
* Hens, B et.al. Mol. Pharmaceutics submitted 2017



GI Buffer Capacity: Very Low

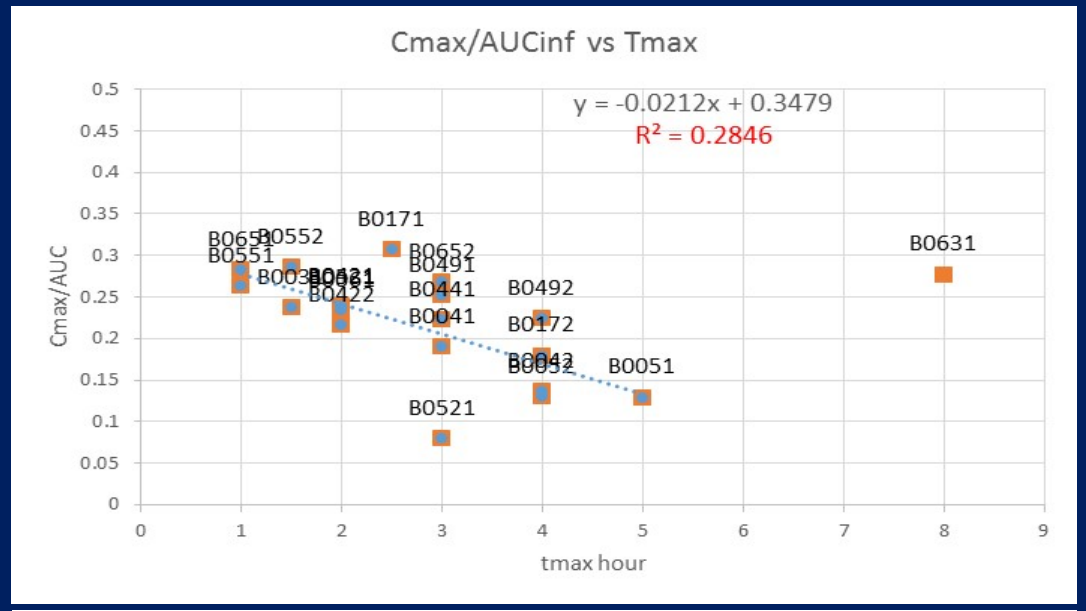


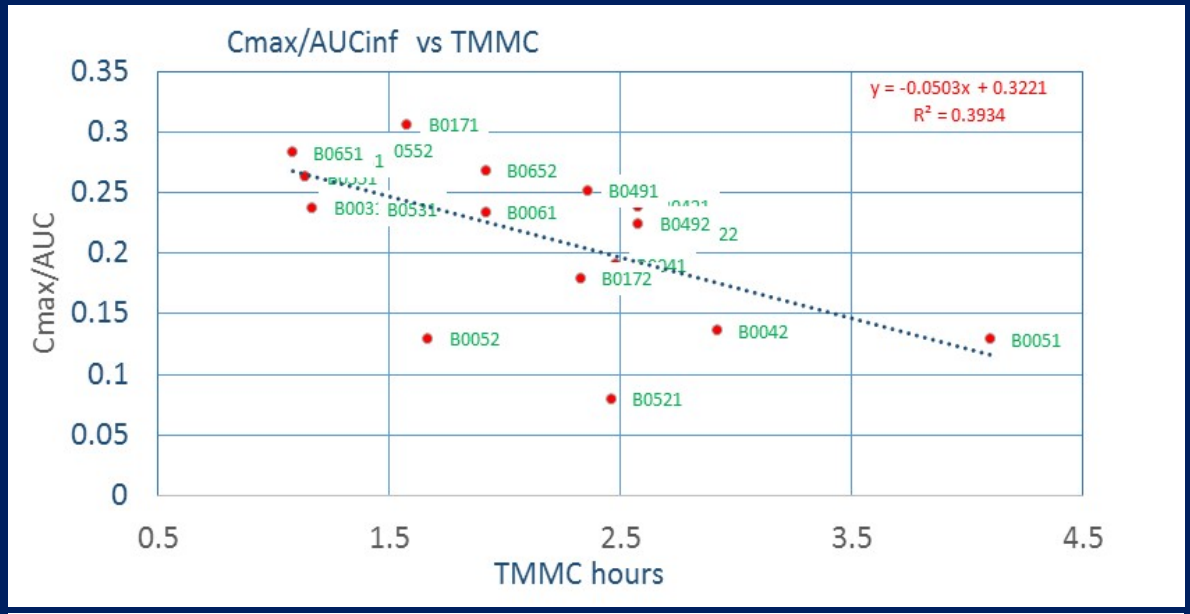
USP Simulated Intestinal Fluid

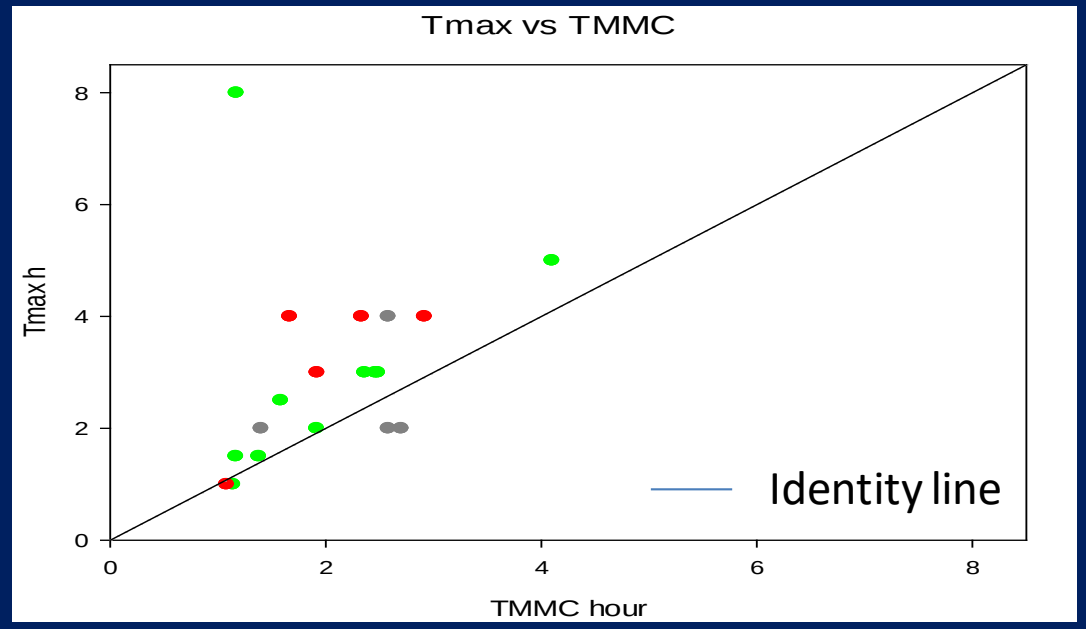
Table 4: Osmolarity, ionic strength and buffer capacity of the two buffers

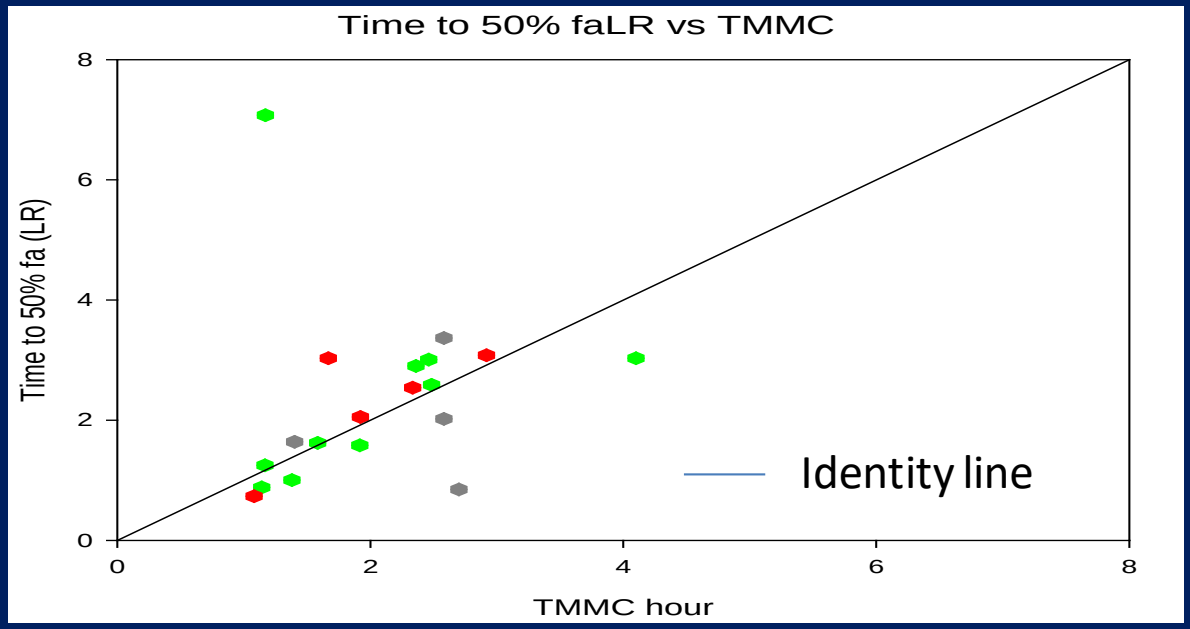
Medium	Osmolarity [mOsmol/kg]	Ionic strength [mol/L]	Buffer capacity [mEq/L/pH unit]
Simulated Intestinal Fluid, pH 6.8 (SIFsp); USP 26	113	0.0720	18.4±0.2
Phosphate Standard Buffer pH 6.8 (IntPh 3)	115	0.0753	18.6±0.1

Exploratory data analysis: Link PK with GI motility, TIII – Post Dose Fasted state

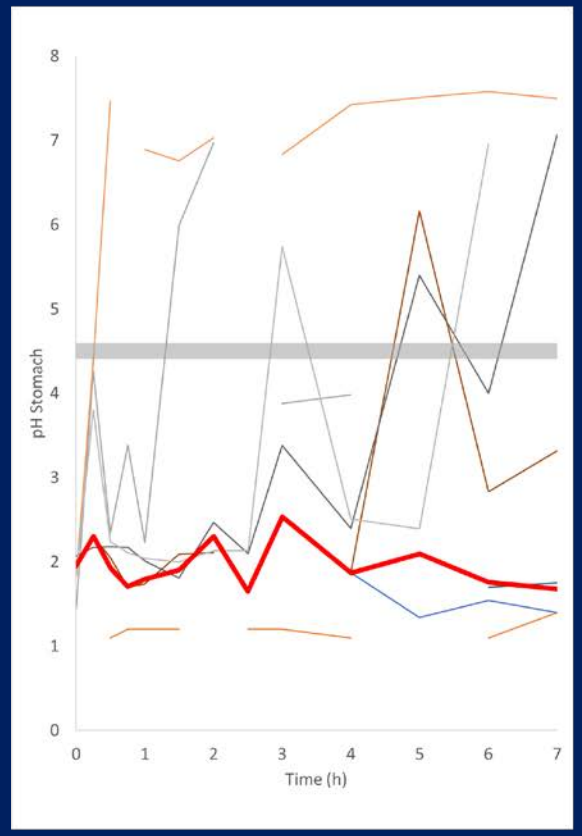


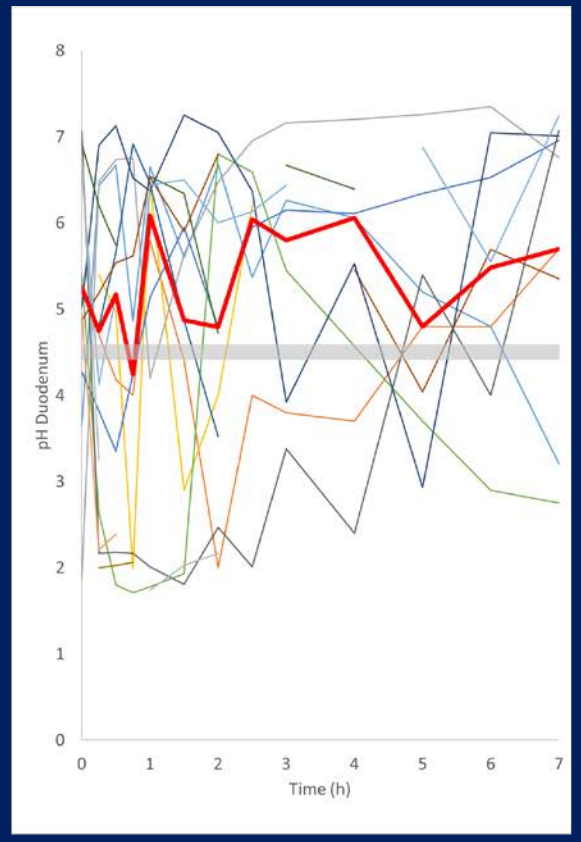


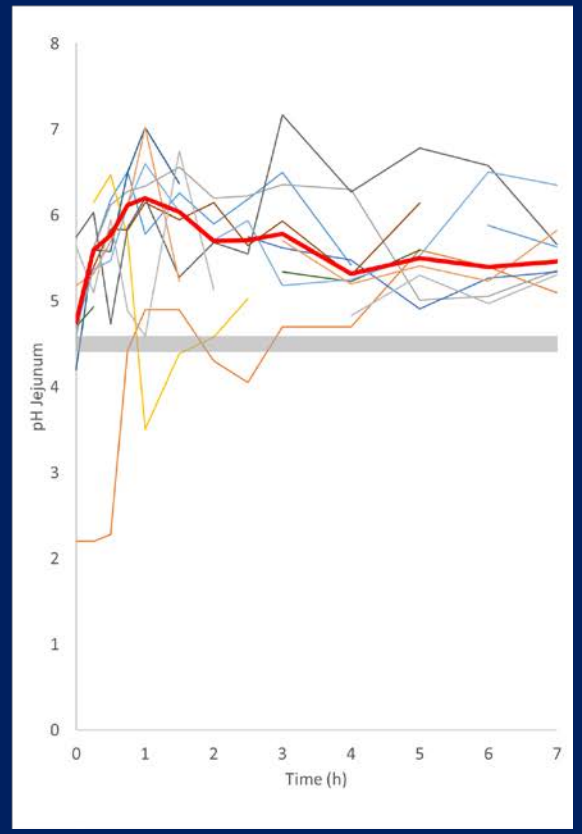




Individual LUMINAL GI pH Fasted state







Stomach

Duodenum

Jejunum

What about the GI Input?

USP Dissolution…Is it that bad?

Depends on drug product

BCS Class and SubClass

- First Step is to Subclassify drugs
- A = Acid
- B = Base
- C = Neutral

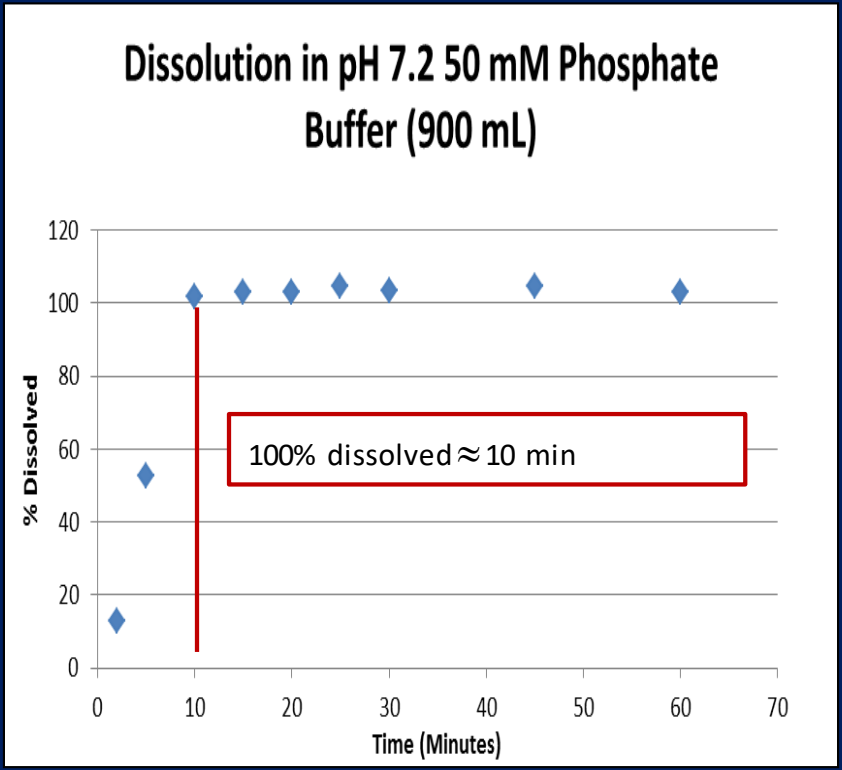
BE Dissolution Proposal (Starting Point)

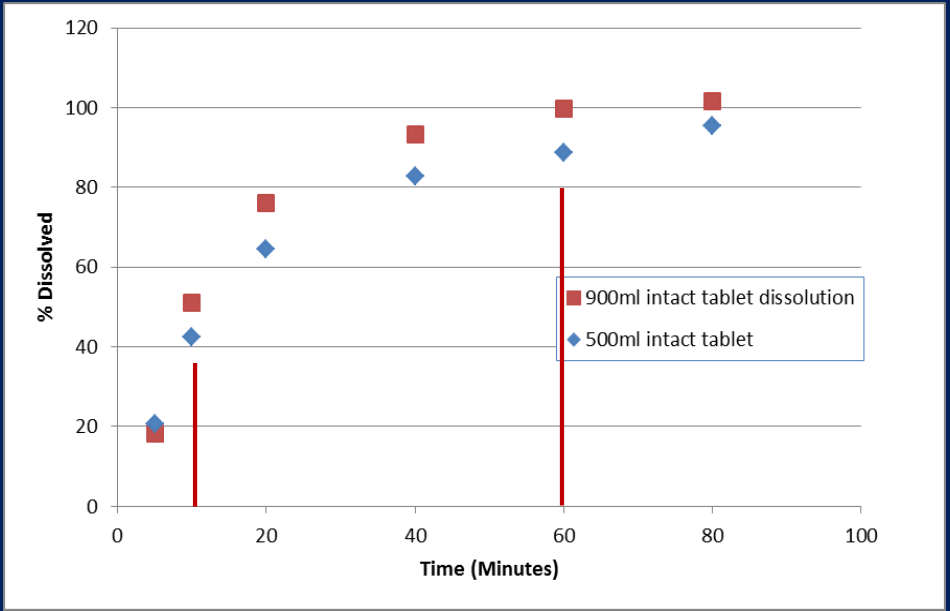
BCS Class	Drug Solubility pH 1.2	Drug Solubility pH 6.8	Drug Permeability	Preferred Procedure
I	High	High	High	>85% Dissolution in 15 min; 30 min, f2., pH = 6.8.
II-A	Low	High	High	15 min at pH=1.2, then 85% Dissolution in 30 min., pH = 6.8; F2>50; 5 points minimum; not more than one point > 85%.
II-B	High	Low	High	>85% Dissolution in 15 min., pH = 1.2.
II-C	Low	Low	High	15 min at pH=1.2; then 85% Dissolution in 30 min., pH = 6.8 plus surfactant*; F2>50; 5 points minimum, not more than one point > 85%.
III	High	High	Low	>85% Dissolution in 15 min., pH = 1.2, 4.5, 6.8.
IV-A	Low	High	Low	15 min. at pH = 1.2; then 85% Dissolution in 30 min., pH = 6.8,; F2>50; 5 points minimum.; not more than one point > 85%.
IV-B	High	Low	Low	>85% Dissolution in 15 min., pH = 1.2.
IV-C	Low	Low	Low	15 min at pH=1.2; then 85% Dissolution in 30 min., pH = 6.8 plus surfactant*; F2>50; 5 points minimum, not more than one point > 85%.

Dissolution of Clinical Dosage form

(800 mg Dr. Reddy's Reference Listed Drug(RLD))

800mg intact tablet dissolution in pH 6.5, 10 mM HCO_3 buffer (15% CO_2 & total buffer concentration of 14 mM). USP 2 apparatus, 50 rpm & 37 °C





Bulk Volume, ml	Extent of dissolution	Time to dissolve 50% dose, min	Time to 100%, min
500	105%	13	80
900	102%	10	60

USP Test: pH =7.2 50mM Phoshate
50 RPM paddle (Apparatus 2)
Not Less Than 80% dissolved in 60 min

BCS Subclass: Absorption Profile

API

- A= Acid
- B=Base
- C=Neutral

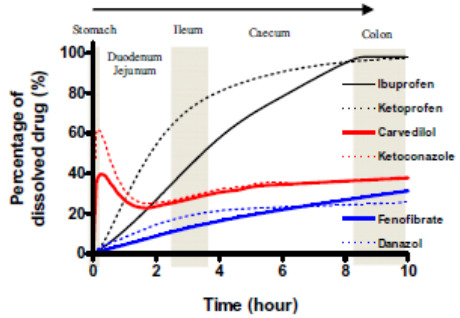


Fig. 2. Percentage of amount dissolved with an IR dosage. Black solid and dot lines represent BCS Class II weak acids, Red solid and dot lines represent BCS class weak bases and blue solid and dot lines represent BCS class neutrals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

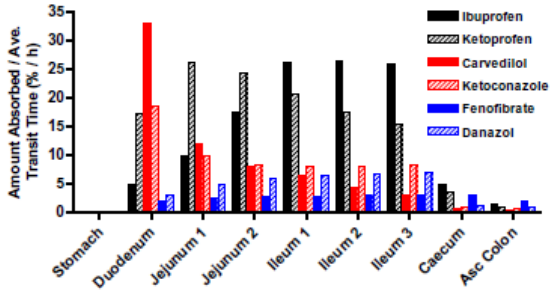


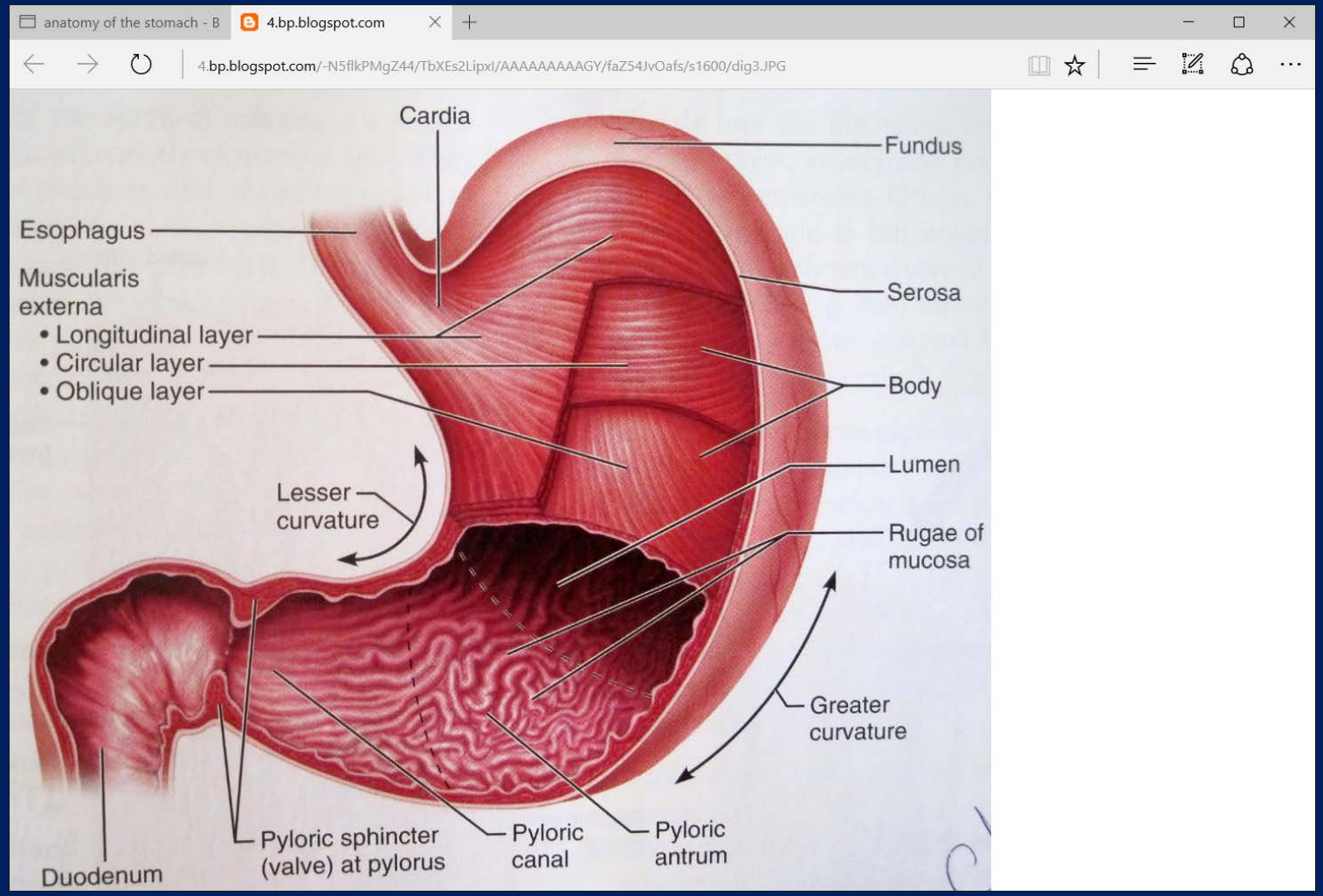
Fig. 3. The absorption rates of BCS Class II drugs in each GI segment. Percentages of amount absorbed after oral administration of an IR dosage are divided by the average transit time and are plotted as a function of each GI segment. Black bars represent BCS Class II weak acids, Red bars represent BCS class weak bases and blue bars represent BCS class neutrals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

BCS SubClasses

BCS Class	0.1 N HCl	pH 6.5	Permeability	Media*
I	High	High	High	PIB**
IIa	Low	High	High	15 and 30 min in PGB** then PIB**
IIb***	High	Low	High	15 or 30 min in PGB** , then PIB**
IIc	Low	Low	High	Dissolution 15 and 30 min in PGB** , Then PIB** + surfactant to match in vivo solubilization
III	High	High	Low	Same as I
IVa	Low	High	Low	Same as IIa
IVb**	High	Low	Low	Same as IIb**
IVc	Low	Low	Low	Same as IIc

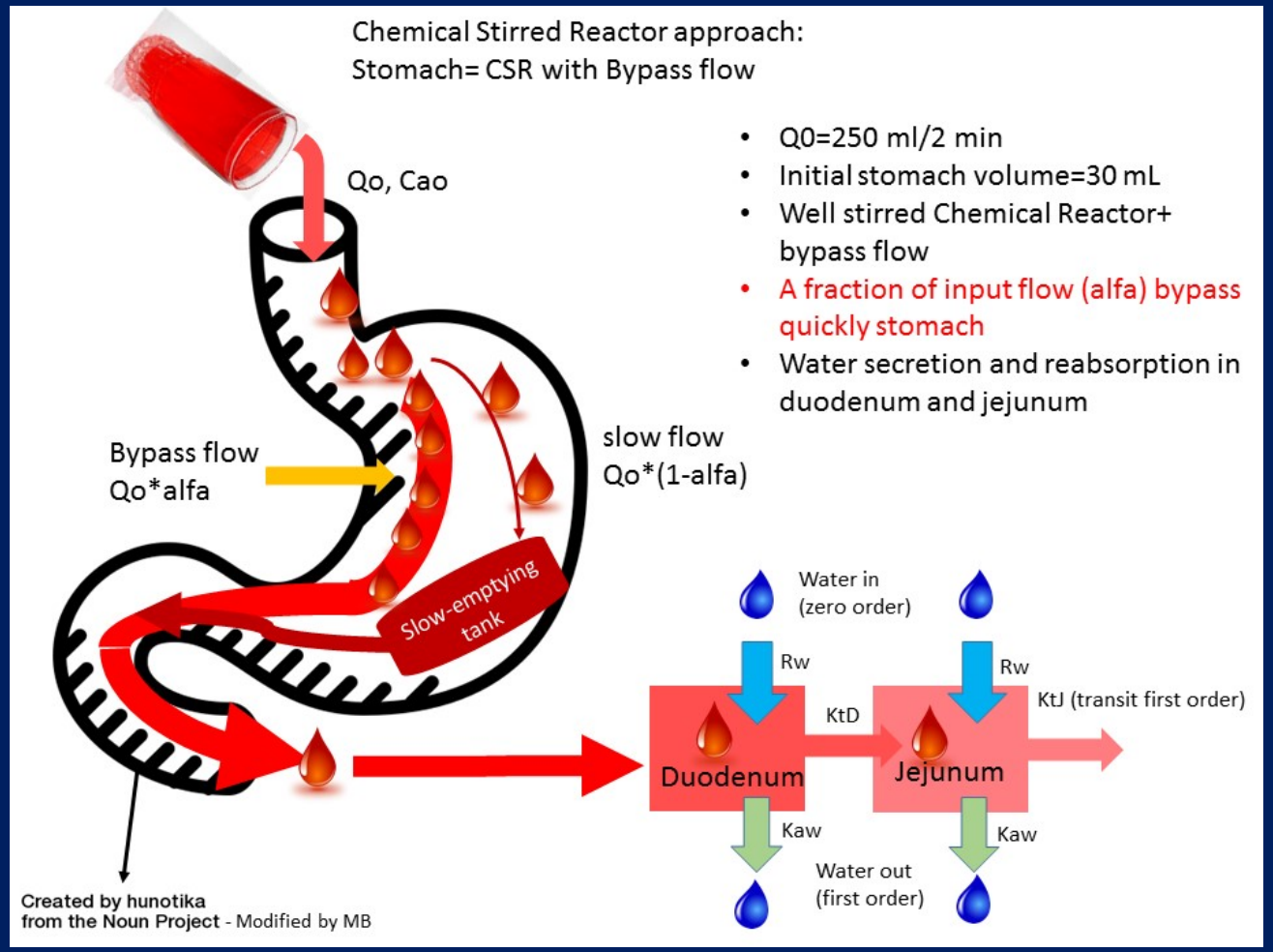
A Key to Prediction is the Input ,I(t), Concentration of Drug at the Absorbing Site(s)

Stomach”: Gastric Emptying (Complex)



More Complex than usually assumed

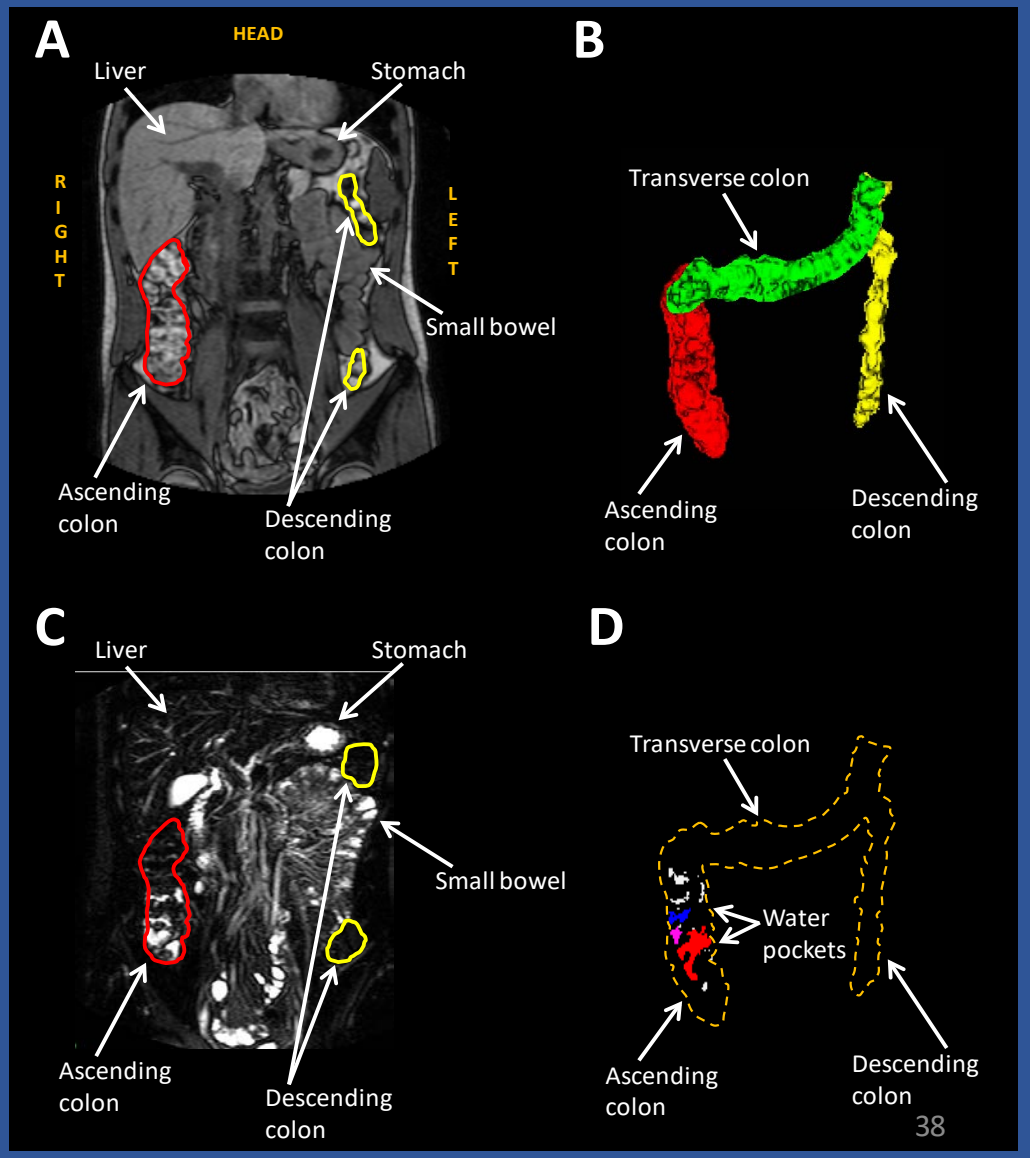
GI Marker (PR) Analysis: Gastric Processing



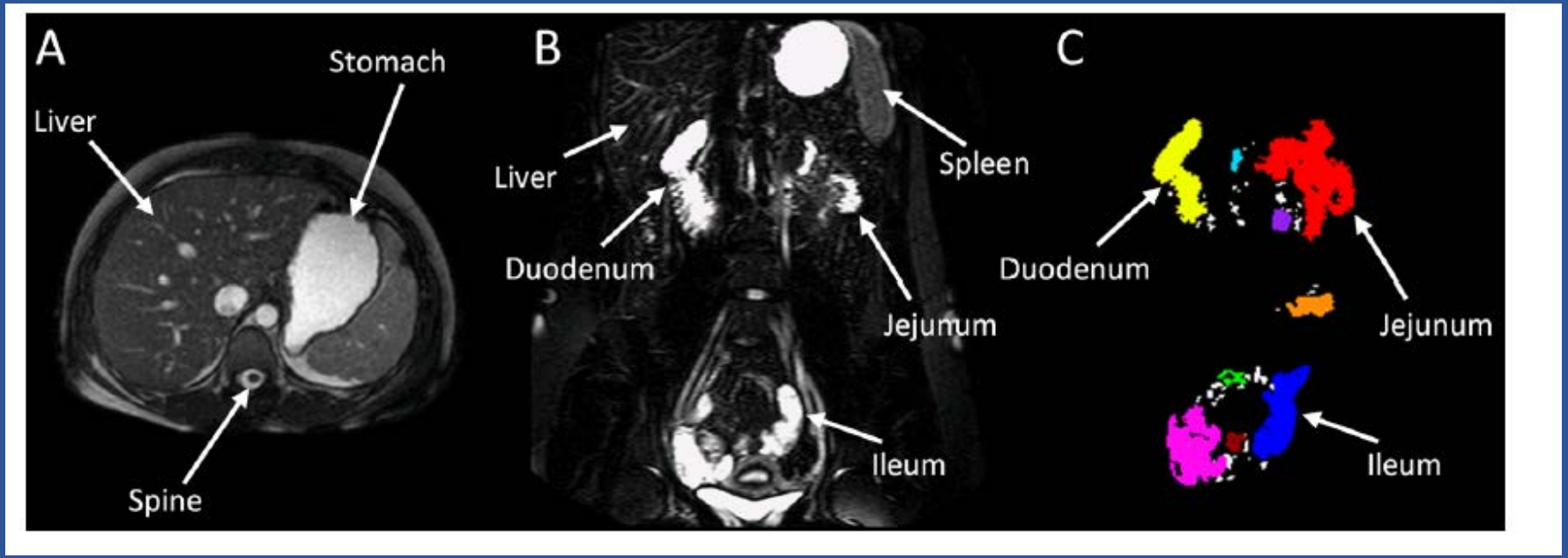
- Multi compartment
  - With bypass
  - Delayed fraction
  - Need Statistical distributions

MRI GI Fluid Study

(Where we are Going)



Gastrointestional Fluid MRI*



*Mudie DM, Murray K, Hoad CL, Pritchard SE, Garnett MC, Amidon GL, Gowland PA, Spiller RC, Amidon GE, Marciani L., Quantification of Gastrointestinal Liquid Volumes and Distribution Following a 240 mL Dose of Water in the Fasted State, Mol Pharm. 2014 Sep 2;11(9):3039-47.

Aqueous Fluid Content of Gastric and Small Intestine after 8oz of Water

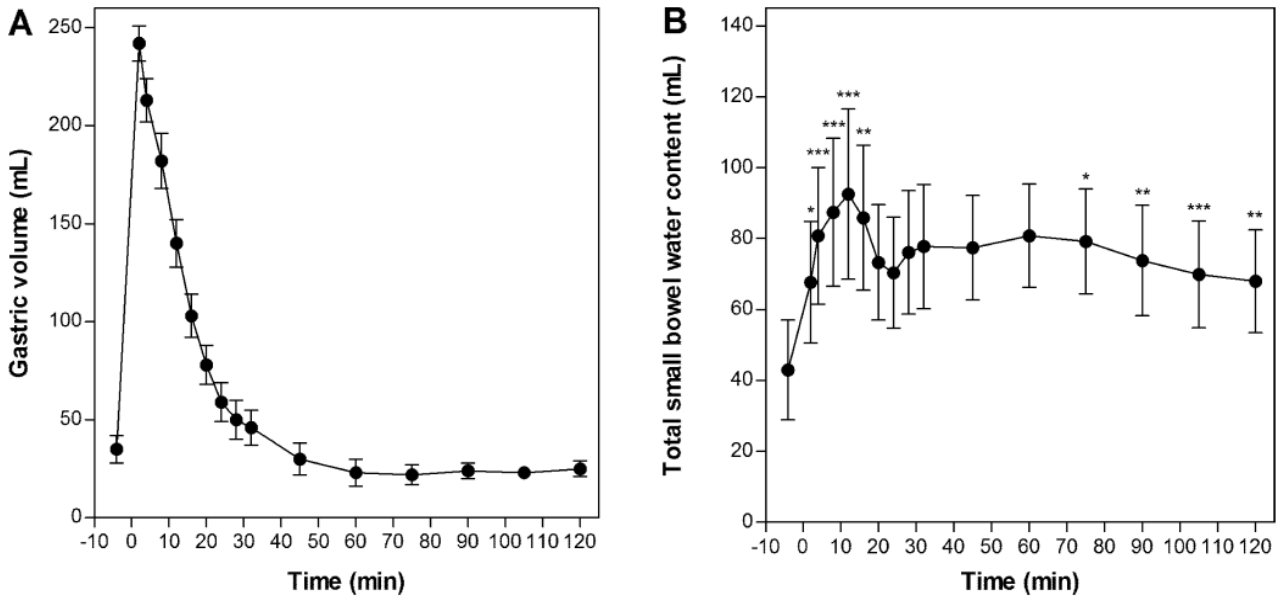


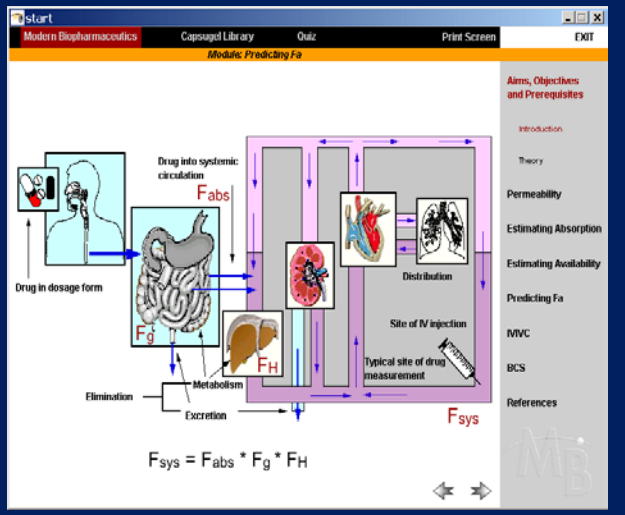
Figure 2. (A) Mean gastric volume and (B) mean total small bowel water content before and after ingestion of a 240 mL dose of water given at $t = 0$ min. $n = 12$ healthy volunteers. Error bars represent ± SEM. Dunn's multiple comparison test versus baseline value * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Error bars represent ± SEM.

Our Goal as Pharmaceutical Scientists

A New Era In Biopharmaceutics

- The Product Science
- Mechanistic
- Can be Predictive
- All Drug Products need BA
- BE is more important than BA

BCS: In Vivo->in Vitro



COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN

New Scientific Directions in Oral Bioequivalence(BE):

Formulation Predictive Dissolution-*In Vivo* Predictive Dissolution

[Implications for Product Development and QC Standards (QbD, PAT, SUPAC, BE)]

Charles R Walgreen, Jr. Professor

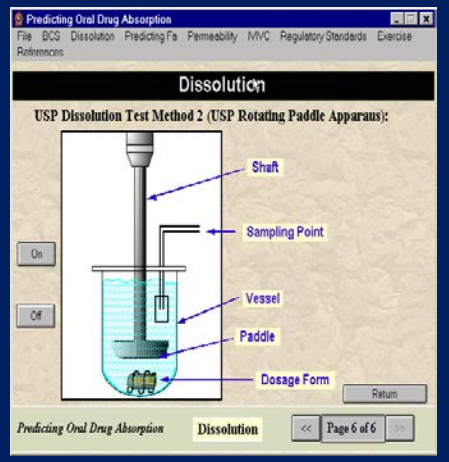
Department of Pharmaceutical Sciences

College of Pharmacy, University of Michigan

Ann Arbor, MI 48109-1065

2010

1970



1950

OrBiTo June 27-29, 2017 : Finland

FDA Project Goal

- GI Sources of Plasma Variability (BE Protocol)
  - pH
  - Buffer
  - Transit/motility/shear rates/viscosity
  - Gastric Mixing/Motility/shear rates/viscosity
- Mass Transport (Computational) Analysis
- Develop in *vitro* tests for Product development (GIS)
  - Formulation Dissolution (Release) *in vitro* Test

Plasma Levels and $F_{abs}(t)$ Ibuprofen

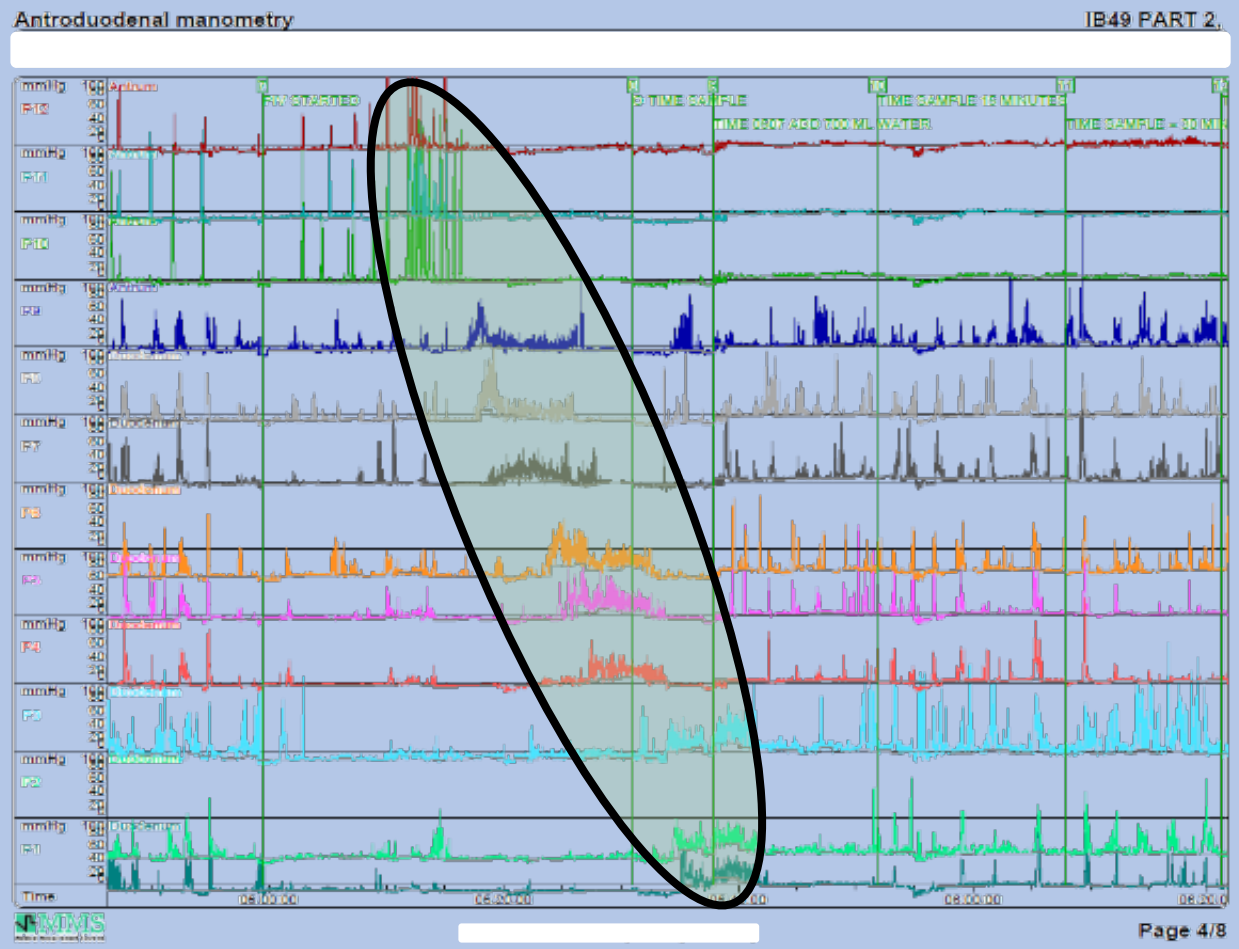
Intubation Plasma Results

- Cmax, Tmax, AUC similar to Literature
- 37 subjects (including repeats)
- Ibuprofen F_{sys} =~99% =F_{abs} (Literature)
  - i.e. no first pass metabolism
- Plasma Elimination from Intubation (this) study similar to literature
- Fabs (8 hr.)_80% at 8 hrs. Fasted and Fed

GI Motility (4 sample and pressure ports) at various sites: Fasted

[Phase I, II, III: BE Study Doses Randomly Relative to Phase)

Motility Phase II III I



Stomach

Duodenum

Proximal Jejunum

Distal Jejunum

GI Motility and Plasma Levels (C_{max})

- Record Motility for 11+ hrs.
  - Begin Motility Recording start up at ~11 PM
- Dose Ibuprofen (RLD) at 4-5 AM
- Record motility and sample for 7 hrs.
- Plasma levels continue at 8, 12, 24 hrs.

Linking IBU Plasma Levels to Gastrointestinal levels and motility/pressure contractions and Propagation

Cmax-GI Motility Conclusions

- Fasted State
  - Cmax most significant Variable is Time to Phase III post dose
  - Intra Subject %CV (~15%) is ½ of inter subject variability (~30%)

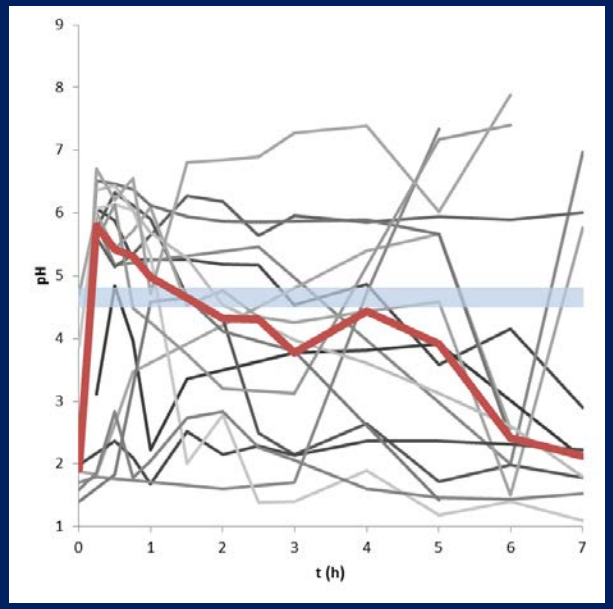
- Fed State
  - Cmax, Tmax most dependent on # of Calories consumed
  - Gastric Emptying and absorption rate determined by motility
  - Intra subject variability (~30%) about equal to Intersubject (~30%)

Other Significant Results

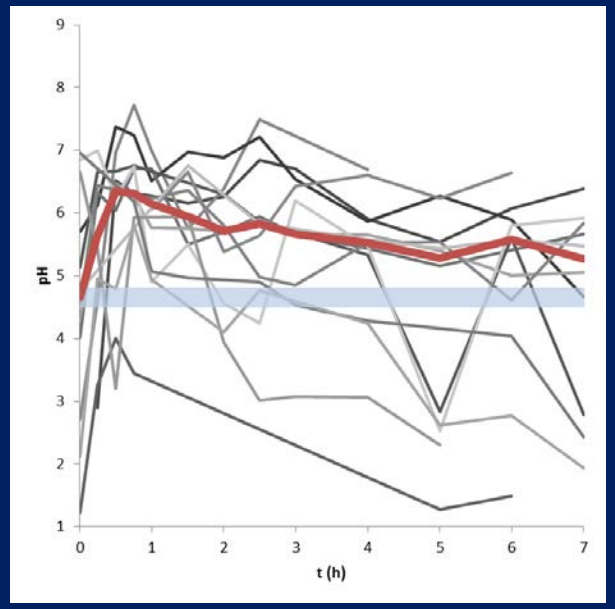
- Ibuprofen in the intestine at 7 hrs.
- pH (variable)
- Buffer capacity (low)

Individual Luminal GI pH (Fed-liquid 

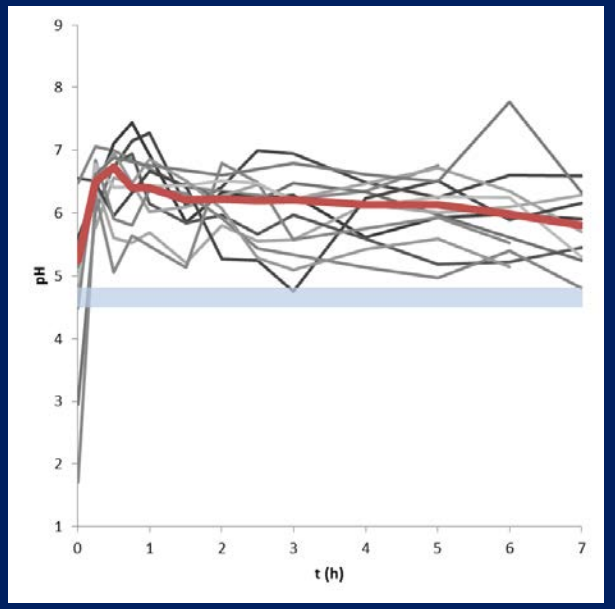
)



Stomach

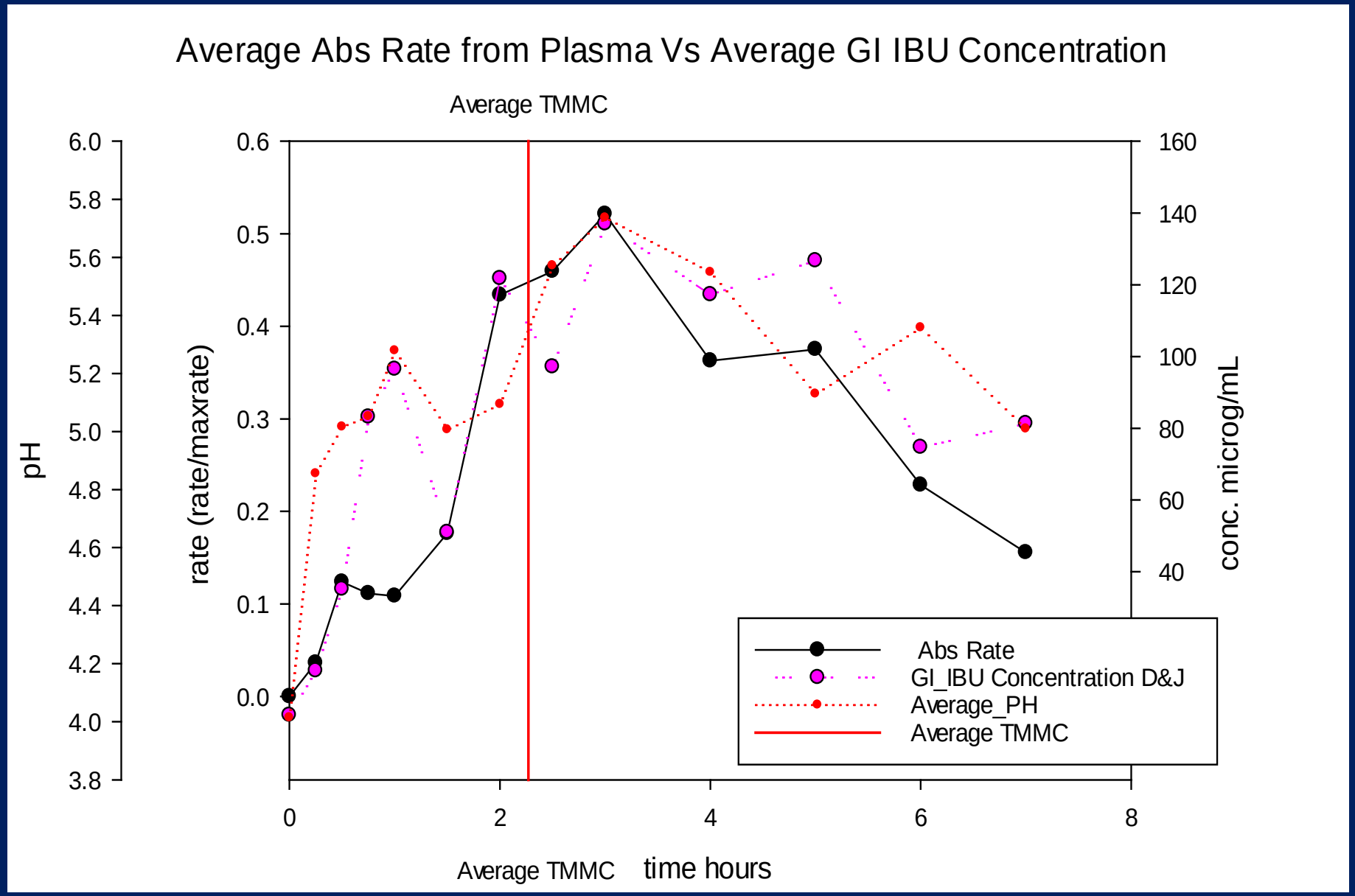


Duodenum



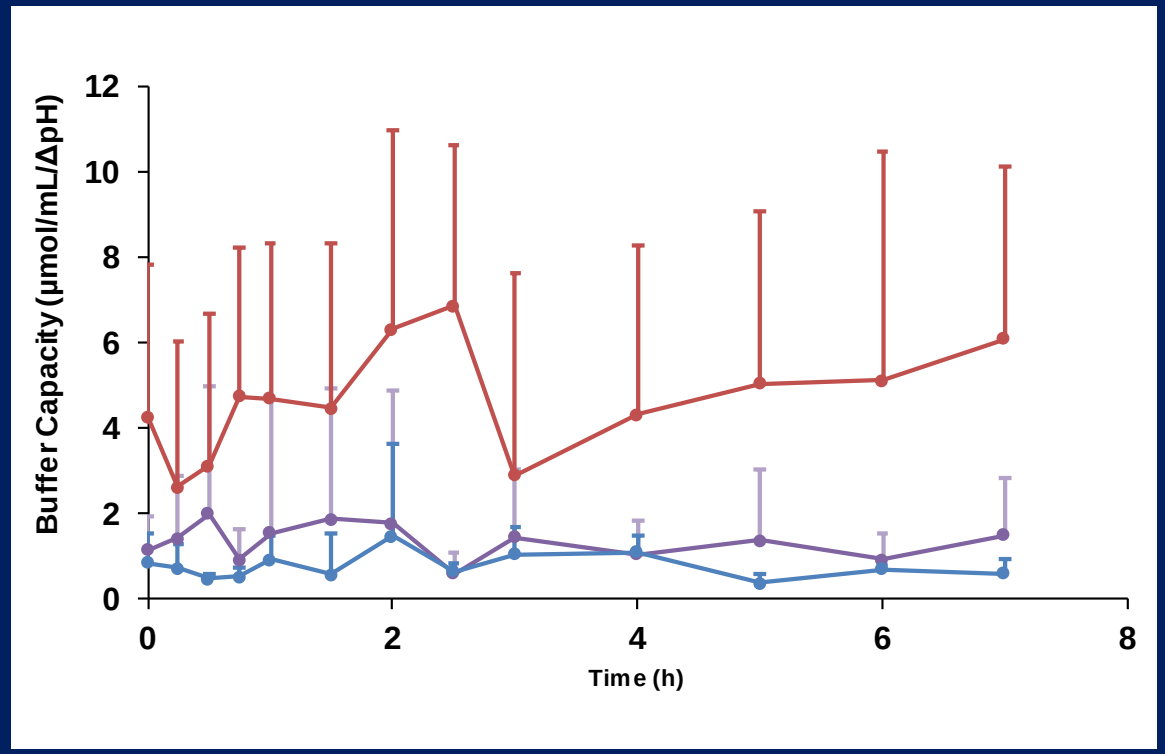
Jejunum

Link PK with GI Ibuprofen concentrations and GI variables

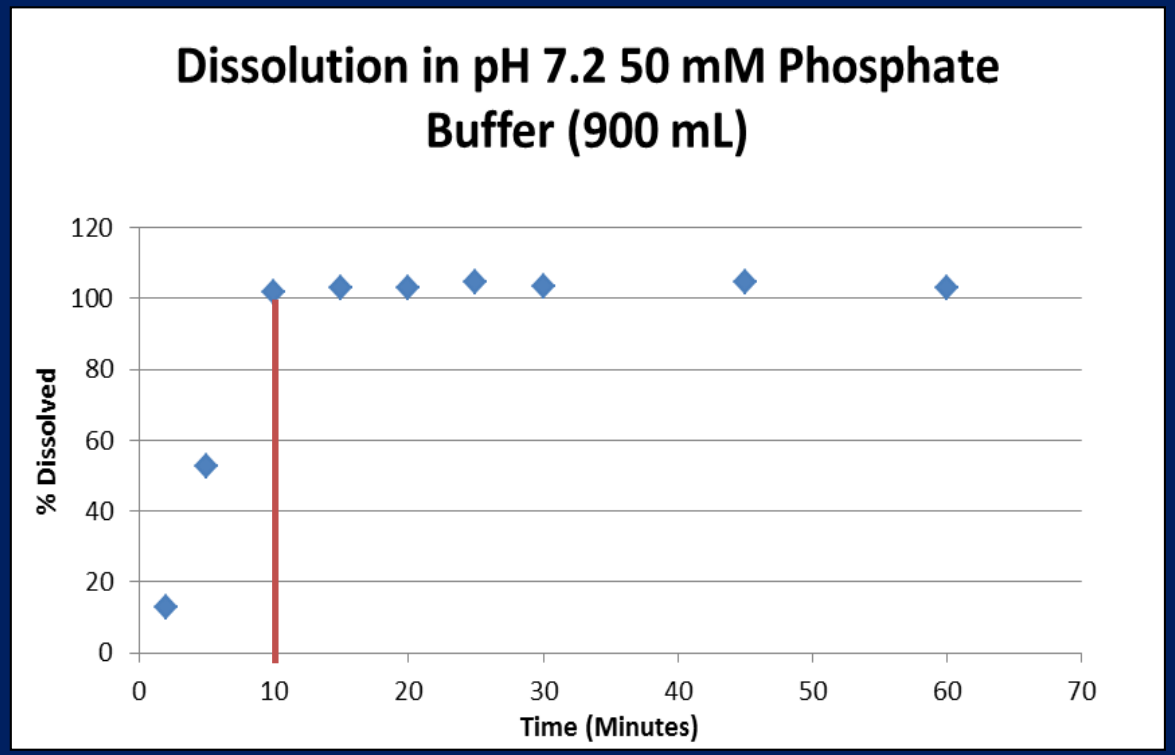


In Vitro-In Vivo

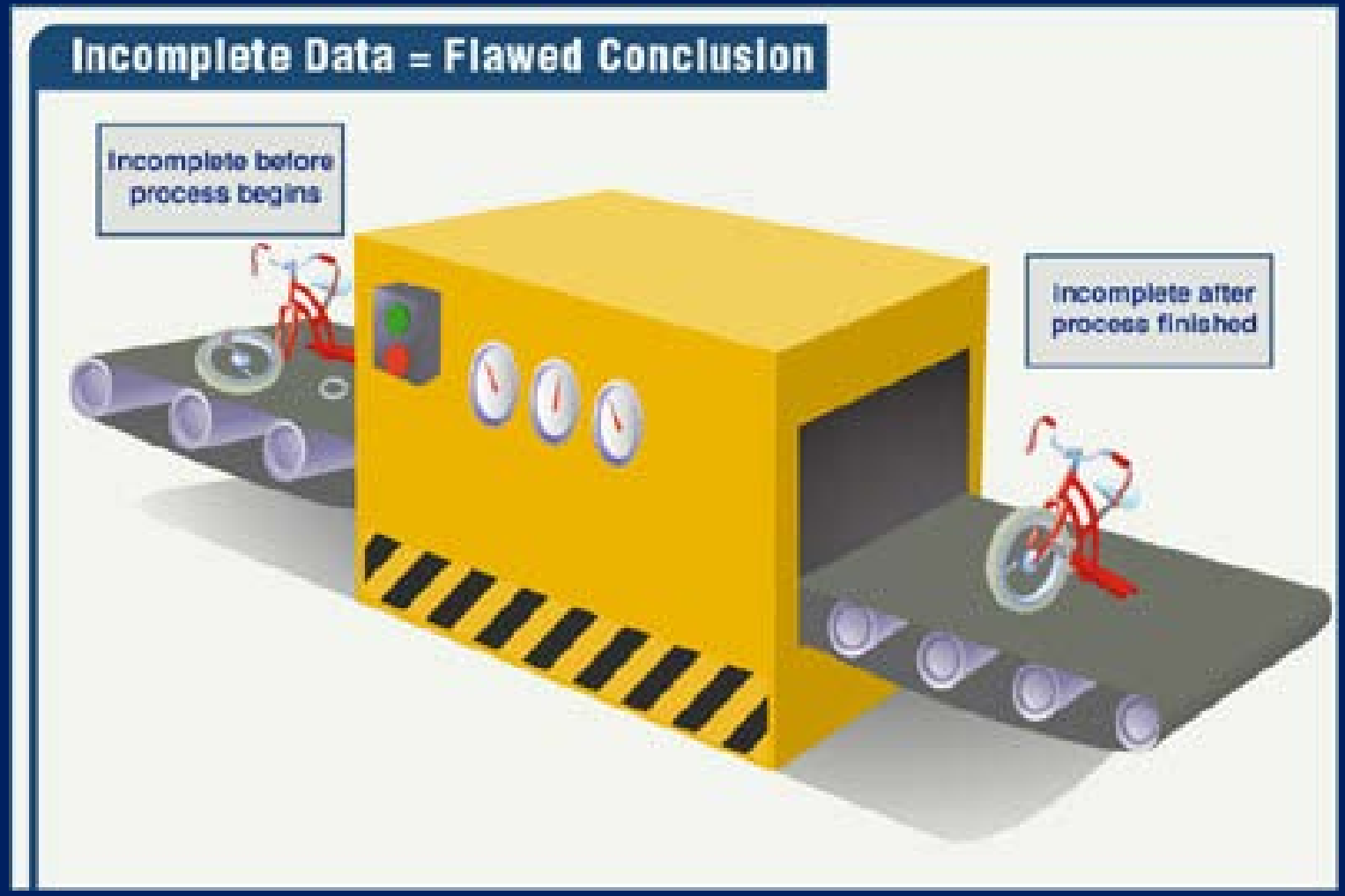
In Vivo



In Vitro (*USP/FDA)



Predictive Absorption: Need Input Function

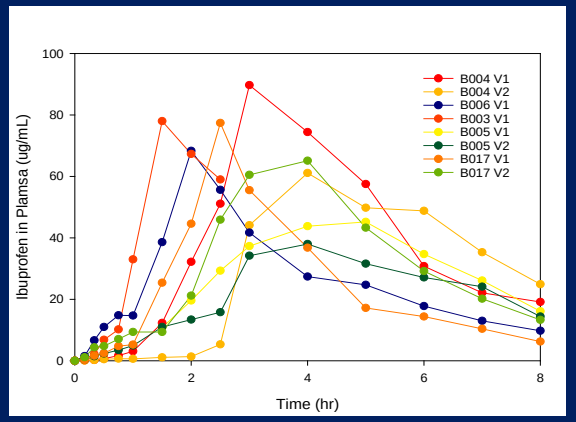


Plasma Deconvolution Results

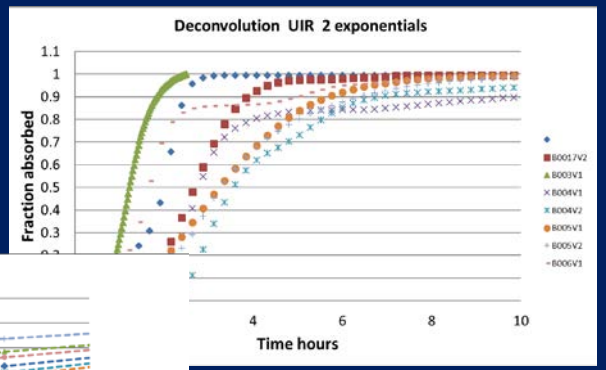
- ~80 Fsys at 8 hrs. (Fasted and Fed)
  - Give actual Results
- => ~20% remaining in intestine
- All PKBIO results => IBU is high permeability

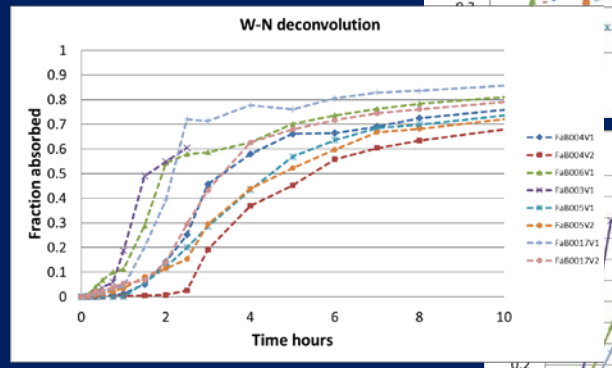
Deconvolution Fasted

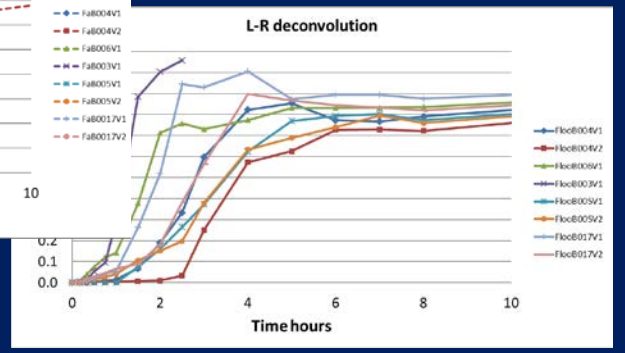
IBU Plasma Levels



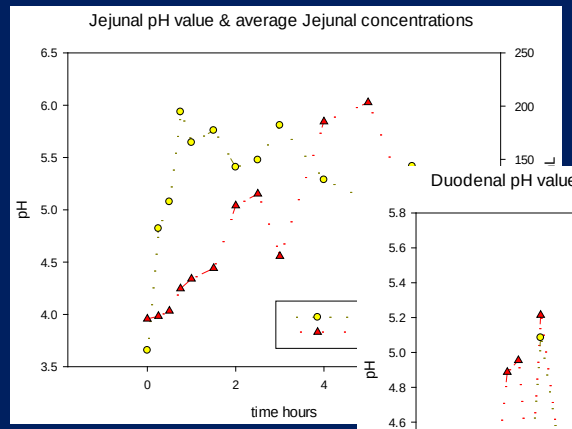
Deconvolution

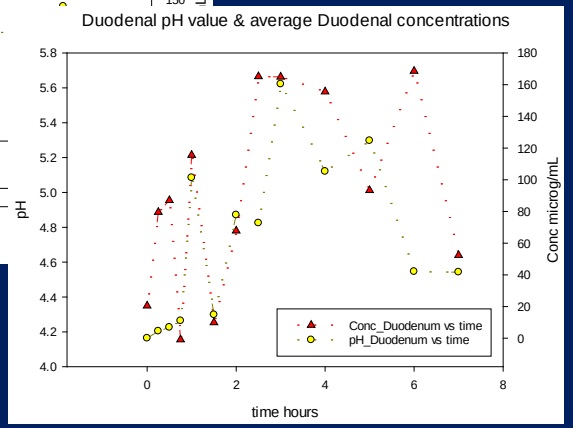






IBU GI concentration & pH values



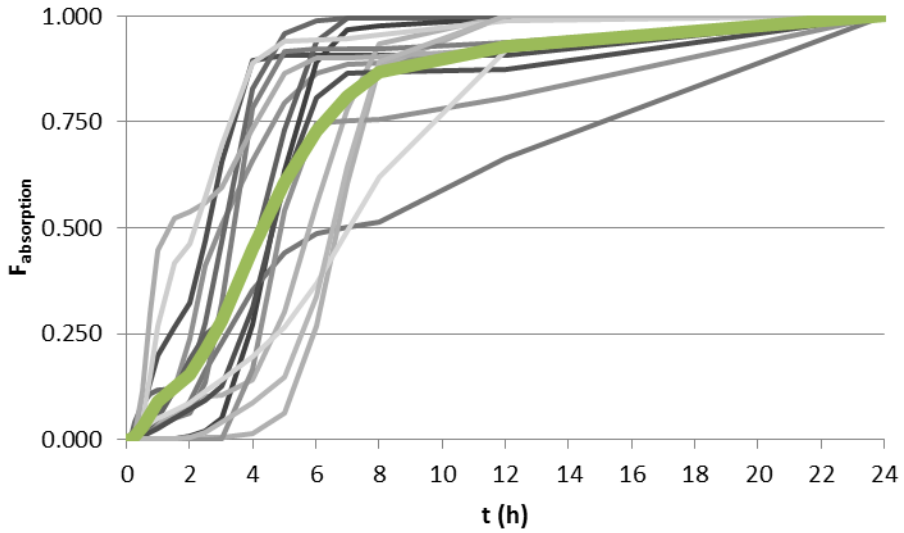


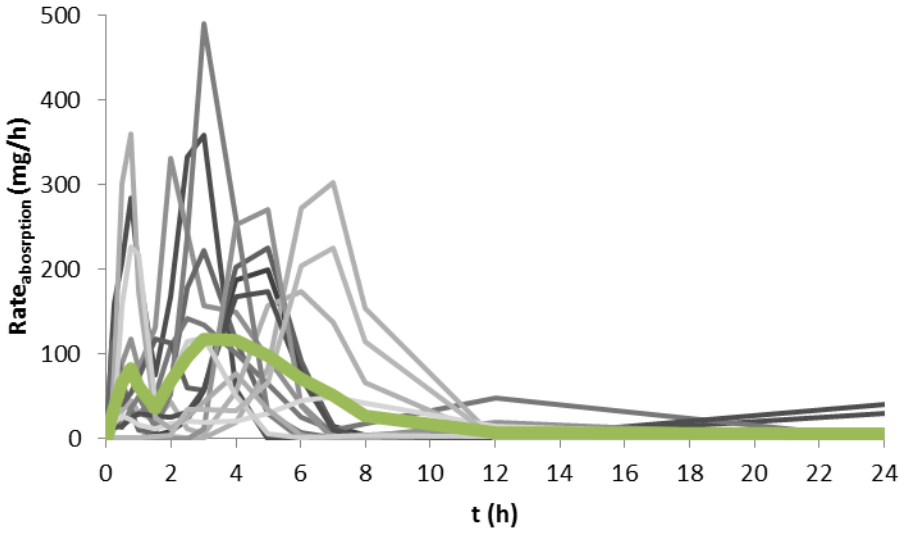
Average Duod&Jejunum

Absorption Rates

Linear interpolation time to time
Average of individual values

Plasma Deconvolution (Fed)



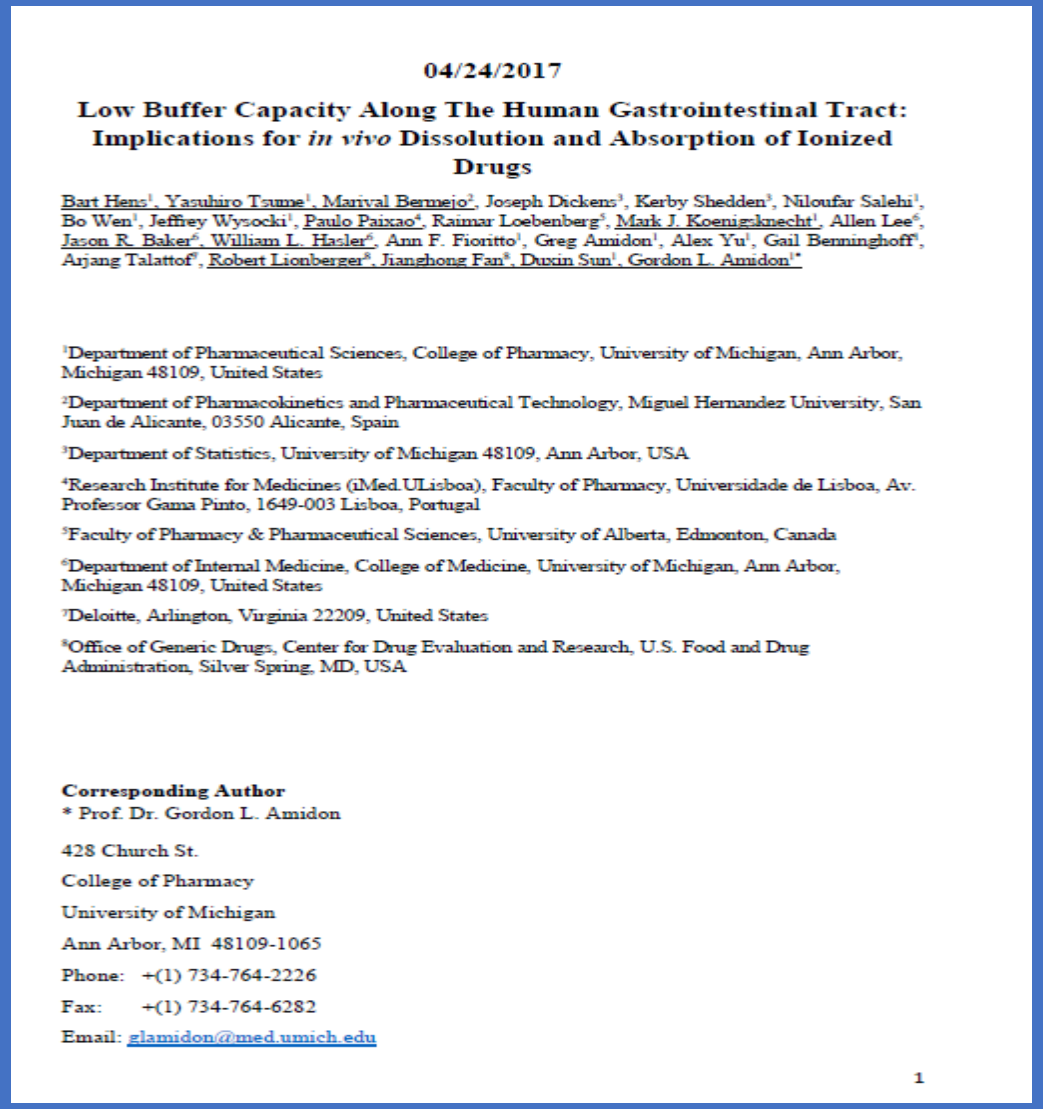


	T25% Abs	T50% Abs	T75% Abs
Subject	**h**	**h**	**h**
B008V1	1.30	2.57	3.22
B020V1	2.02	2.95	4.61
B020V2	2.45	3.05	3.70
B022V1	3.94	4.63	5.38
B022V2	3.12	7.01	13.68
B026V1	4.75	5.78	6.82
B031V1	2.54	4.15	5.04
B034V1	5.95	6.67	7.39
B041V1	2.83	3.31	3.89
B043V1	3.74	4.66	5.62
B043V2	4.22	4.90	6.14
B046V1	4.80	7.01	9.26
B060V1	0.67	1.20	4.08
B060V2	0.91	2.21	3.22
B066V1	5.66	6.53	7.34
Mean	3.26	4.44	5.96
CV%	51	42	46
Min	0.67	1.20	3.22
Max	5.95	7.01	13.68

Deconvolution Summary

- ~80% absorbed at 8 hrs.
- => 20% still in the intestine
- T(50%) Fasted=
- T(50%) Fed = 4.4 hr.

An Unexpected Result: Low GI Buffer Capacity*



04/24/2017

Low Buffer Capacity Along The Human Gastrointestinal Tract: Implications for *in vivo* Dissolution and Absorption of Ionized Drugs

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[2]Department of Pharmacokinetics and Pharmaceutical Technology, Miguel Hernandez University, San Juan de Alicante, 03550 Alicante, Spain

[3]Department of Statistics, University of Michigan 48109, Ann Arbor, USA

[4]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Professor Gama Pinto, 1649-003 Lisboa, Portugal

[5]Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Canada

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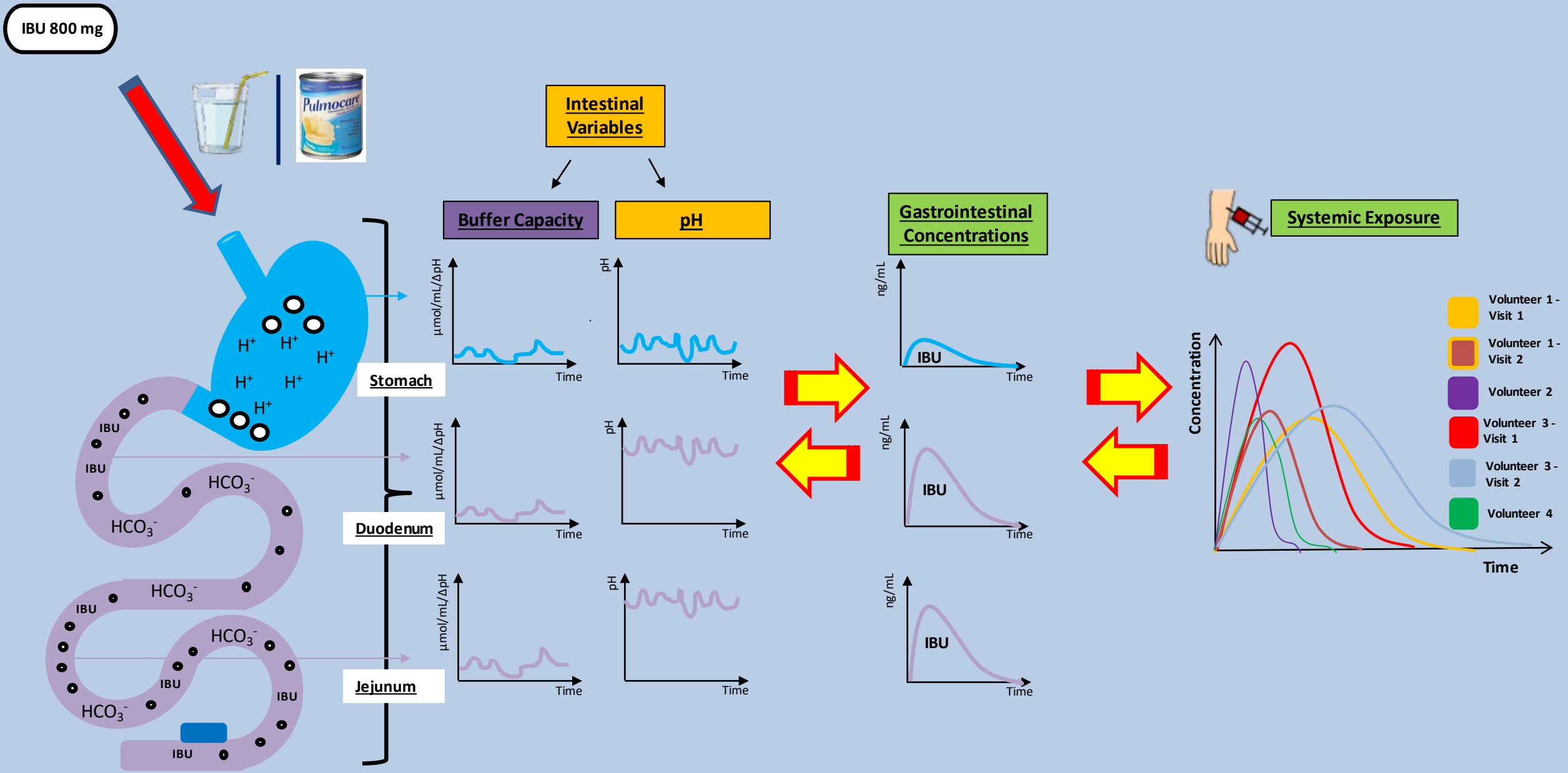
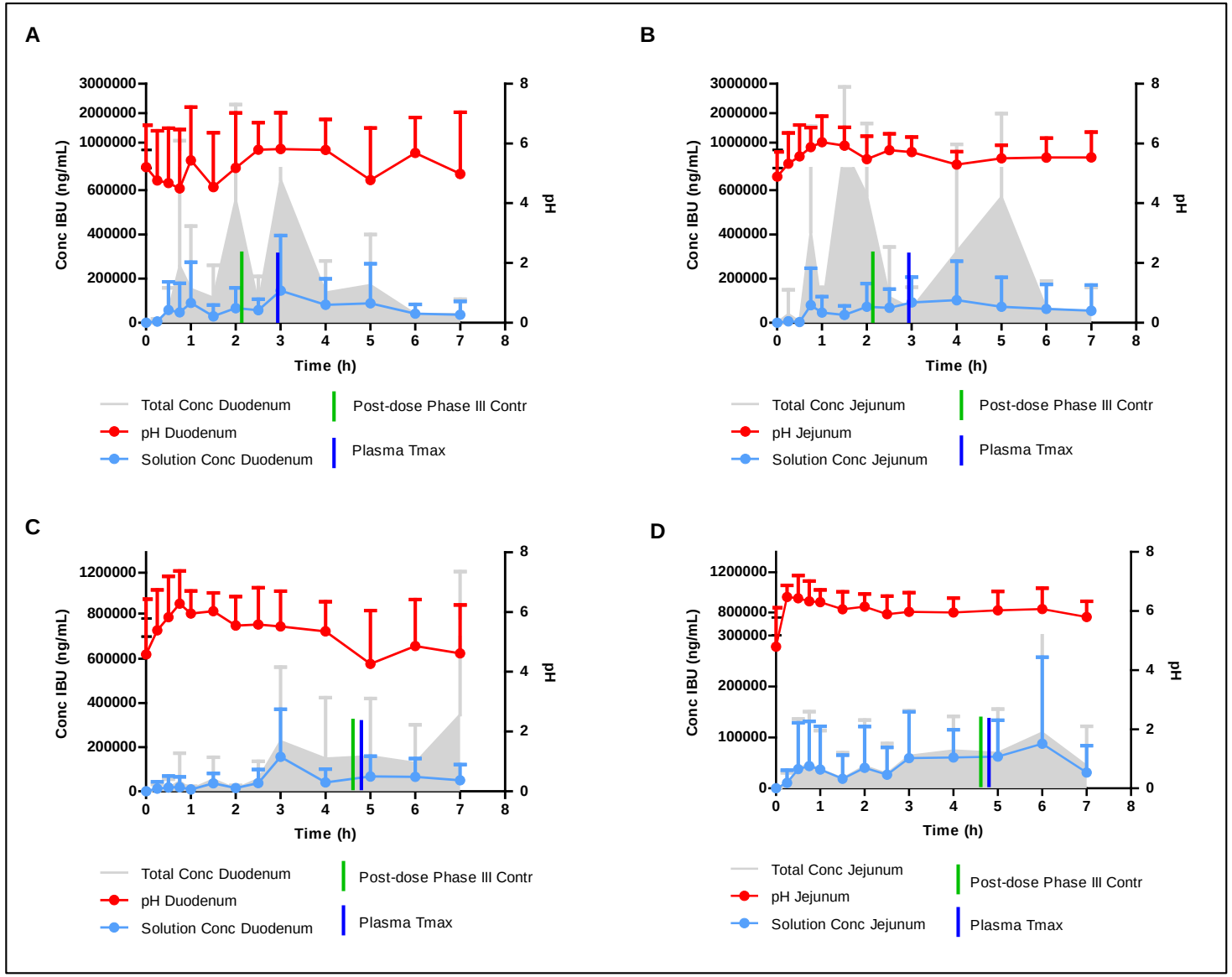
* Hens, B et.al. Mol. Pharmaceutics submitted 2017


IBU 800 mg
Pulmocare
Intestinal Variables
Buffer Capacity
pH
Gastrointestinal Concentrations
Systemic Exposure
Stomach
Duodenum
Jejunum
H+
IBU
HCO3-
µmol/mL/ΔpH
pH
ng/mL
Time
Concentration
Volunteer 1 - Visit 1
Volunteer 1 - Visit 2
Volunteer 2
Volunteer 3 - Visit 1
Volunteer 3 - Visit 2
Volunteer 4

Measured Gastrointestinal pH & Ibuprofen Levels

Fasted (A,B)

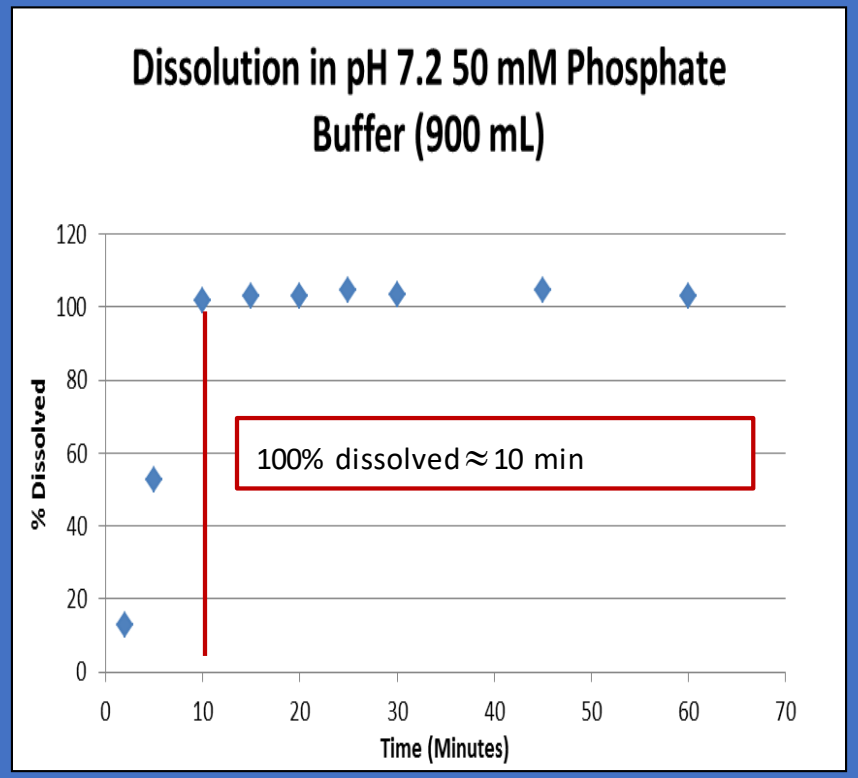
Fed(C,D)

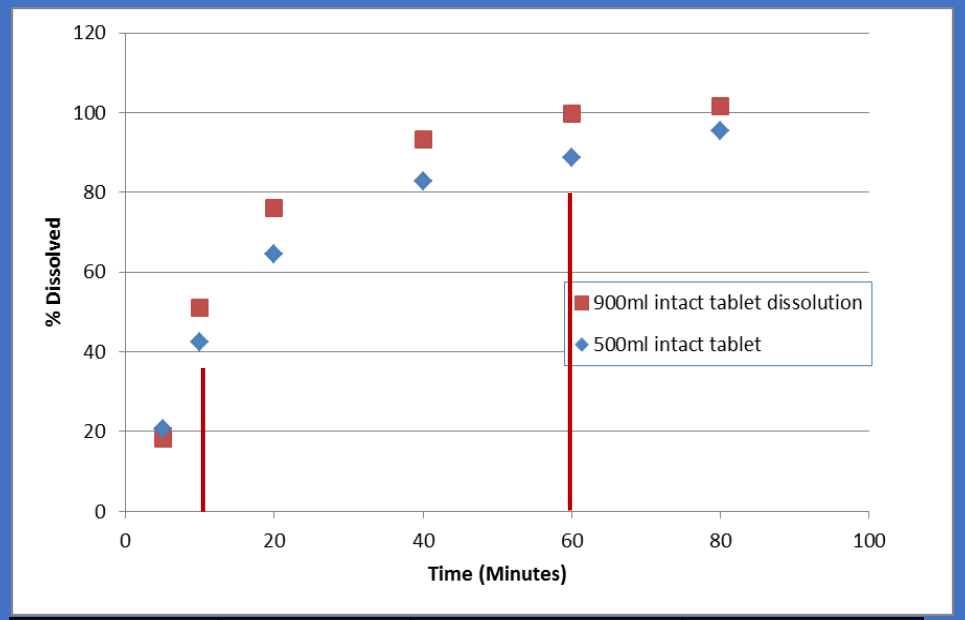


Dissolution of Clinical Dosage form

(800 mg Dr. Reddy's Reference Listed Drug(RLD))

800mg intact tablet dissolution in pH 6.5, 10 mM HCO_3 buffer (15% CO_2 & total buffer concentration of 14 mM). USP 2 apparatus, 50 rpm & 37 °C





Bulk Volume, ml	Extent of dissolution	Time to dissolve 50% dose, min	Time to 100%, min
500	105%	13	80
900	102%	10	60

USP Test: pH =7.2 50mM Phoshate
50 RPM paddle (Apparatus 2)
Not Less Than 80% dissolved in 60 min

Gastrointestinal pH & Ibuprofen Levels

Fasted (A,B)

Fed(C,D)

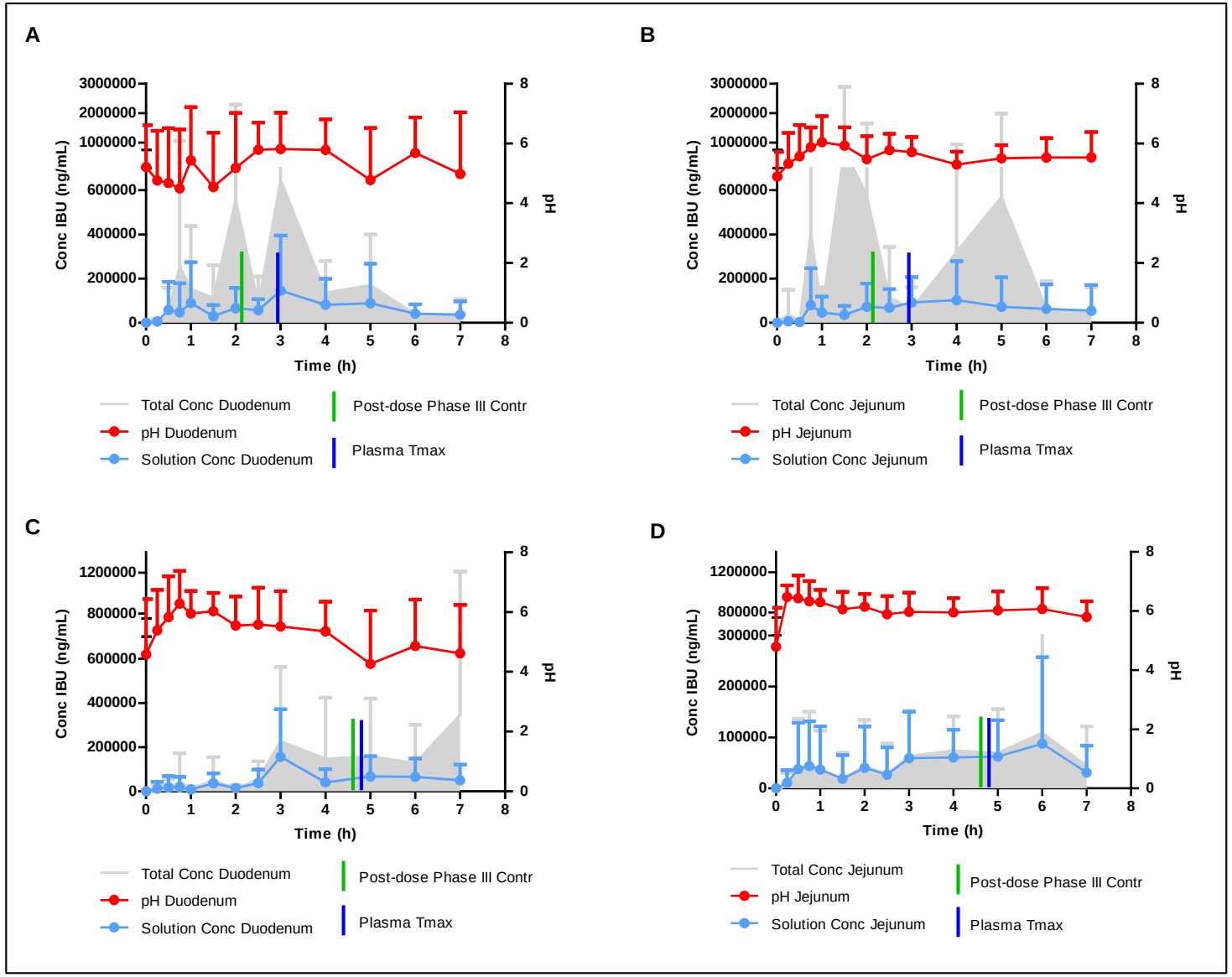
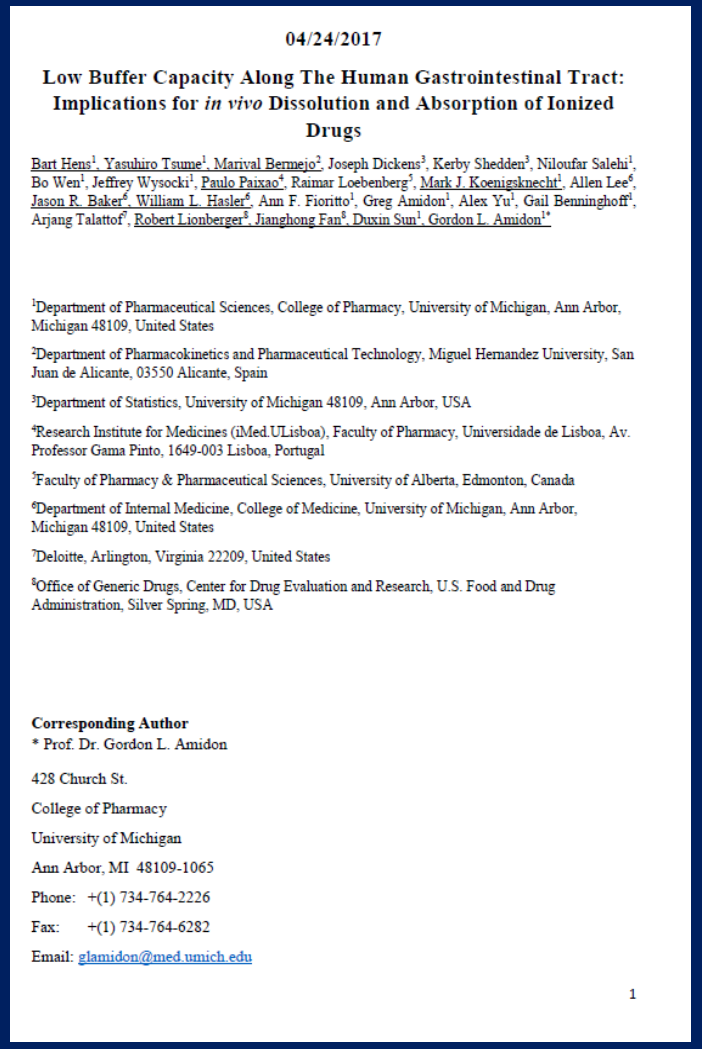


Table 4: Osmolarity, ionic strength and buffer capacity of the two buffers

Medium	Osmolarity [mOsmol/kg]	Ionic strength [mol/L]	Buffer capacity [mEq/L/pH unit]
Simulated Intestinal Fluid, pH 6.8 (SIFsp); USP 26	113	0.0720	18.4±0.2
Phosphate Standard Buffer pH 6.8 (IntPh 3)	115	0.0753	18.6±0.1

GI Buffer Capacity



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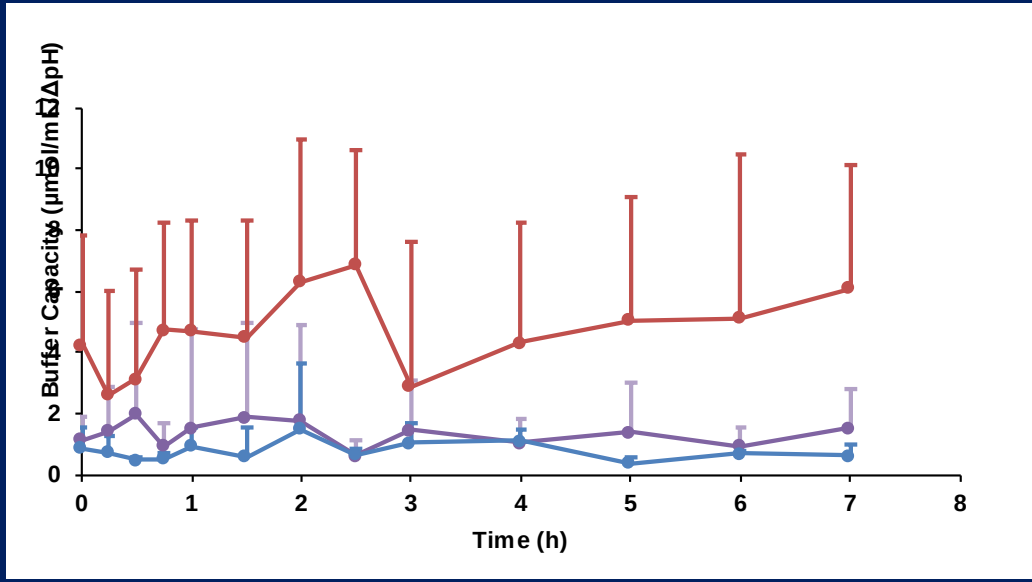
1

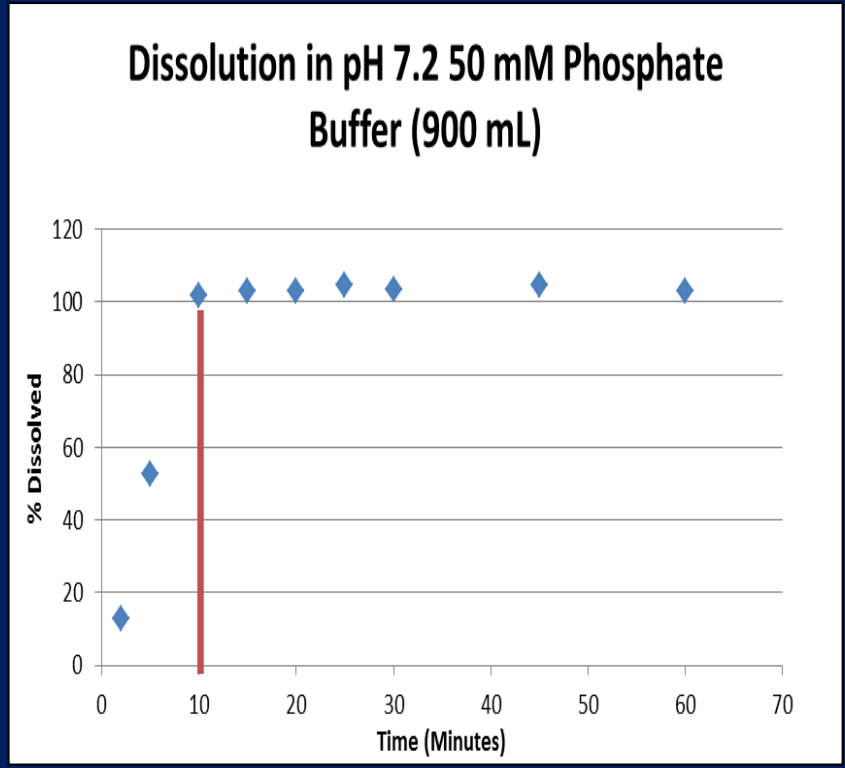
- Submitted to Mol Pharmaceutics
  - OrBiTo Special Issue
  - Largest Effort (in history) in Biopharmaceutical Sciences
- New Era in Oral Biopharmaceutics
- => Other Routes
- Physiological-Physical-Material at the site of Application

In Vitro-In Vivo

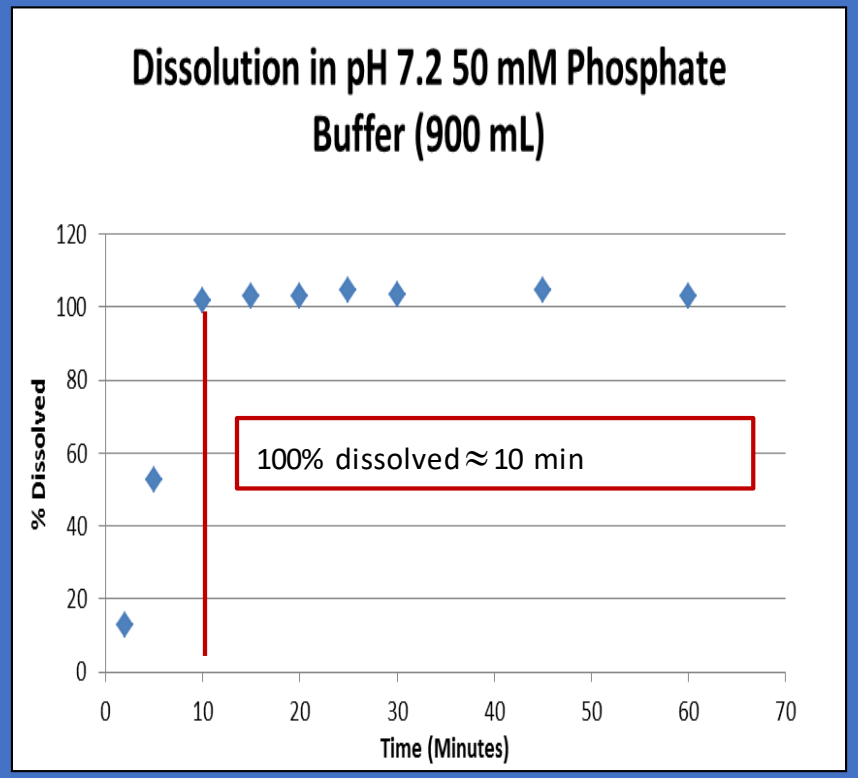
In Vivo



In Vitro (*USP/FDA)



Dissolution of Clinical Dosage form
(800 mg Dr. Reddy's Reference Listed Drug(RLD))



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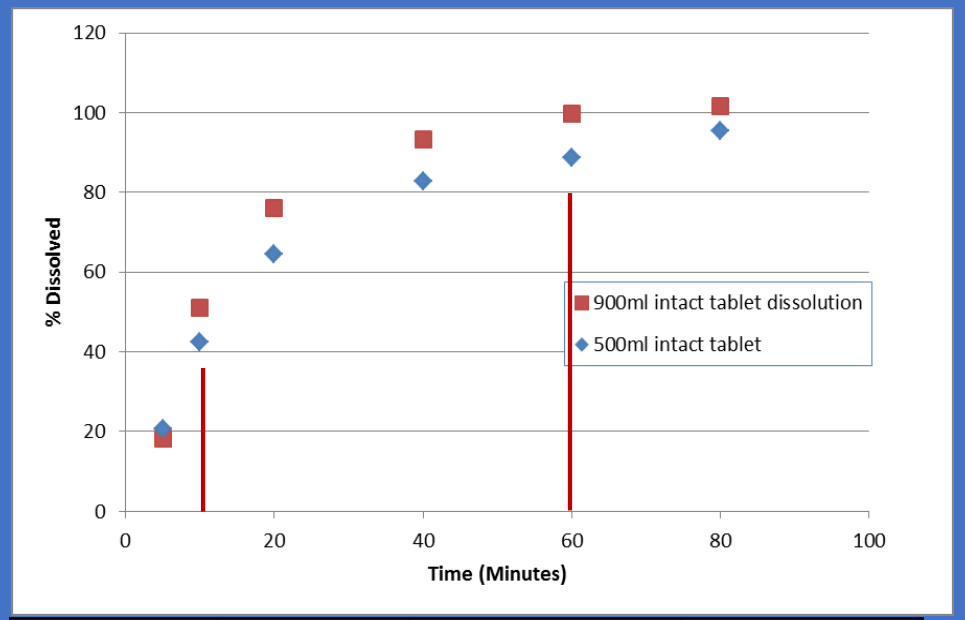
800mg intact tablet dissolution in pH 6.5, 10 mM HCO_3 buffer (15% CO_2 & total buffer concentration of 14 mM). USP 2 apparatus, 50 rpm & 37 °C



Bulk Volume, ml	Extent of dissolution	Time to dissolve 50% dose, min	Time to 100%, min
500	105%	13	80
900	102%	10	60

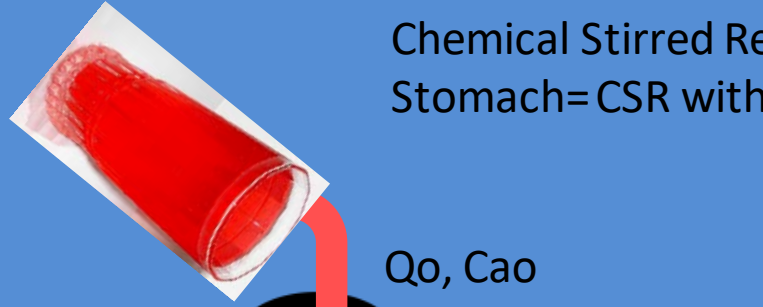
Other Results

- Stomach is very complicated

Marker (Phenol Red)

- Observed at 15 min in Duodenum and Jejunum
  - A by-pass ‘channel’
- Indicates Net Fluid change at that Position and Time
- Not absorbed (<10%)
- Present in Stomach at 7 hrs.
  - Slow emptying ‘dead’ space

Chemical Stirred Reactor approach:
Stomach= CSR with Bypass flow

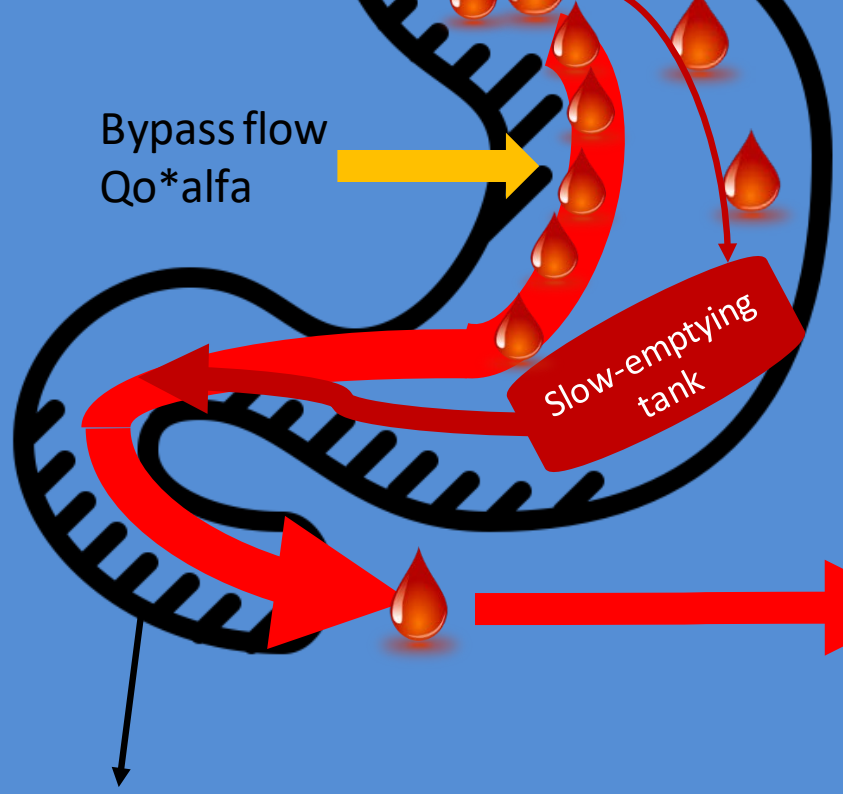


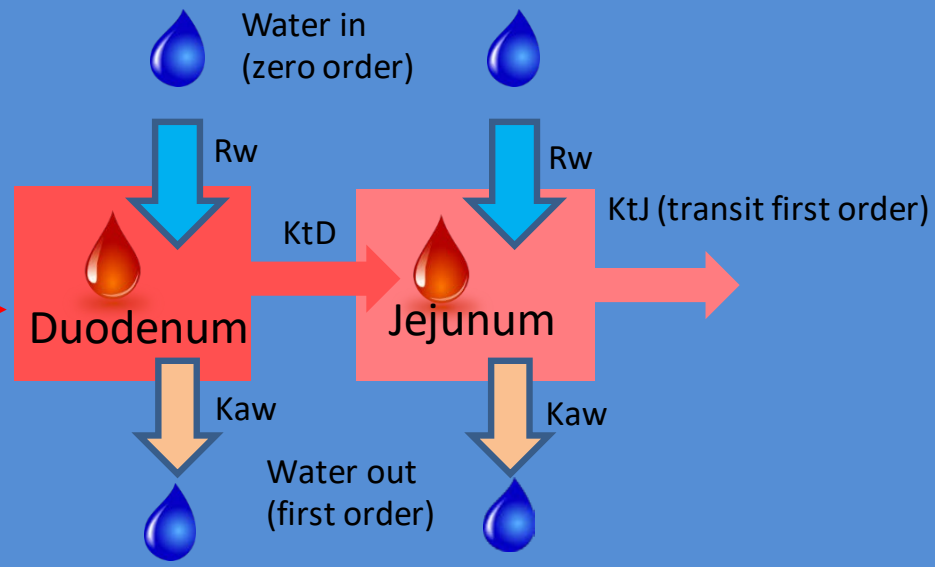
Qo, Cao

- Q0=250 ml/2 min
- Initial stomach volume=30 mL
- Well stirred Chemical Reactor+ bypass flow
- A fraction of input flow (alfa) bypass quickly stomach
- Water secretion and reabsorption in duodenum and jejunum
- Gastric secretion included

Bypass flow
Qo*alfa

slow flow
Qo*(1-alfa)





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from the Noun Project - Modified by MB

Gastrointestinal Fluid Volume

molecular pharmaceutics

Article

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Quantification of Gastrointestinal Liquid Volumes and Distribution Following a 240 mL Dose of Water in the Fasted State

Deanna M. Mudie,[†] Kathryn Murray,[‡] Caroline L. Hoad,[‡] Susan E. Pritchard,[‡] Martin C. Garnett,[§] Gordon L. Amidon,[†] Penny A. Gowland,[‡] Robin C. Spiller,[∥] Gregory E. Amidon,[†] and Luca Marciani*[,∥]

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[‡]Sir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, University of Nottingham, Nottingham NG7 2RD, United Kingdom

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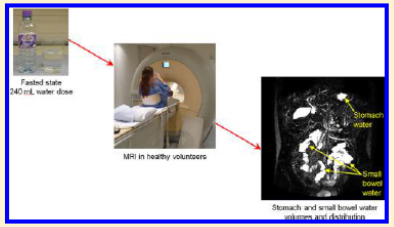
Supporting Information

ABSTRACT: The rate and extent of drug dissolution and absorption from solid oral dosage forms is highly dependent upon the volumes and distribution of gastric and small intestinal water. However, little is known about the time courses and distribution of water volumes *in vivo* in an undisturbed gut. Previous imaging studies offered a snapshot of water distribution in fasted humans and showed that water in the small intestine is distributed in small pockets. This study aimed to quantify the volume and number of water pockets in the upper gut of fasted healthy humans following ingestion of a glass of water (240 mL, as recommended for bioavailability/bioequivalence (BA/BE) studies), using recently validated noninvasive magnetic resonance imaging (MRI) methods.



Twelve healthy volunteers underwent upper and lower abdominal MRI scans before drinking 240 mL (8 fluid ounces) of water. After ingesting the water, they were scanned at intervals for 2 h. The drink volume, inclusion criteria, and fasting conditions matched the international standards for BA/BE testing in healthy volunteers. The images were processed for gastric and intestinal total water volumes and for the number and volume of separate intestinal water pockets larger than 0.5 mL. The fasted stomach contained 35 ± 7 mL (mean ± SEM) of resting water. Upon drinking, the gastric fluid rose to 242 ± 9 mL. The gastric water volume declined rapidly after that with a half emptying time ($T_{50\%}$) of 13 ± 1 min. The mean gastric volume returned back to baseline 45 min after the drink. The fasted small bowel contained a total volume of 43 ± 14 mL of resting water. Twelve minutes after ingestion of water, small bowel water content rose to a maximum value of 94 ± 24 mL contained within 15 ± 2 pockets of 6 ± 2 mL each. At 45 min, when the glass of water had emptied completely from the stomach, total intestinal water volume was 77 ± 15 mL distributed into 16 ± 3 pockets of 5 ± 1 mL each. MRI provided unprecedented insights into the time course, number, volume, and location of water pockets in the stomach and small intestine under conditions that represent standard BA/BE studies using validated techniques. These data add to our current understanding of gastrointestinal physiology and will help improve physiological relevance of *in vitro* testing methods and *in silico* transport analyses for prediction of bioperformance of oral solid dosage forms, particularly for low solubility Biopharmaceutics Classification System (BCS) Class 2 and Class 4 compounds.

KEYWORDS: *gastric emptying, intestinal water, bioperformance, dissolution, small bowel, MRI*

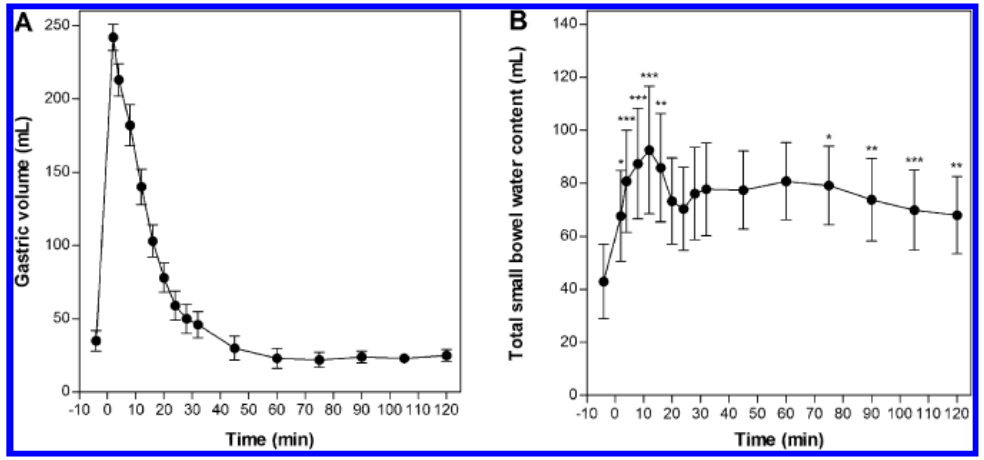


Figure 2. (A) Mean gastric volume and (B) mean total small bowel water content before and after ingestion of a 240 mL dose of water given at $t = 0$ min. $n = 12$ healthy volunteers. Error bars represent ± SEM. Dunn's multiple comparison test versus baseline value * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Error bars represent ± SEM.

New Scientific Directions in Oral Bioequivalence: Implications for Product Development, QbD, PAT, and QC

- Gastrointestinal (GI) Variables→ Drug Absorption→ Systemic Availability (Bioavailability)
  - What is controlling GI Drug Absorption/Systemic Availability (Cmax, AUC)
- We are performing Direct Simultaneous GI Measurement:
  - GI catheter and Plasma sampling
  - Variables, pH, Buffer, Motility, plasma levels (Fasted/Fed)
- Magnetic Resonance Imaging of GI fluid (MRI of GI water)
  - Validation of Catheter Results with MRI Results
  - Extend to pediatric, patients
- *In Vivo* Predictive Dissolution (iPD) Methodology

Where To Go ?

- New BE Science
- All Routes: Interaction of Product with site of Application
- Local Effects of Product (formulation)
  - Direct product on changing Membrane
  - Changes of Product at Site
- Much more Careful Dissolution
- Separate Formulation Dissolution (iPD) from QC Dissolution

Scientific Starting Point: Biopharmaceutics at Site of Application (All Routes)

$$M(t) = \int_0^t \iint_A (P_{eff} \cdot C)\, dA\, dt$$

Absorption per unit area per unit time

Diffusion vs. Pharmacokinetic Views of (Oral) Absorption

Diffusion/Transport

$$J = (dM / dt)1 / A$$
$$= P \cdot \Delta C \cong P \cdot C$$
$$P = cm / \sec.$$

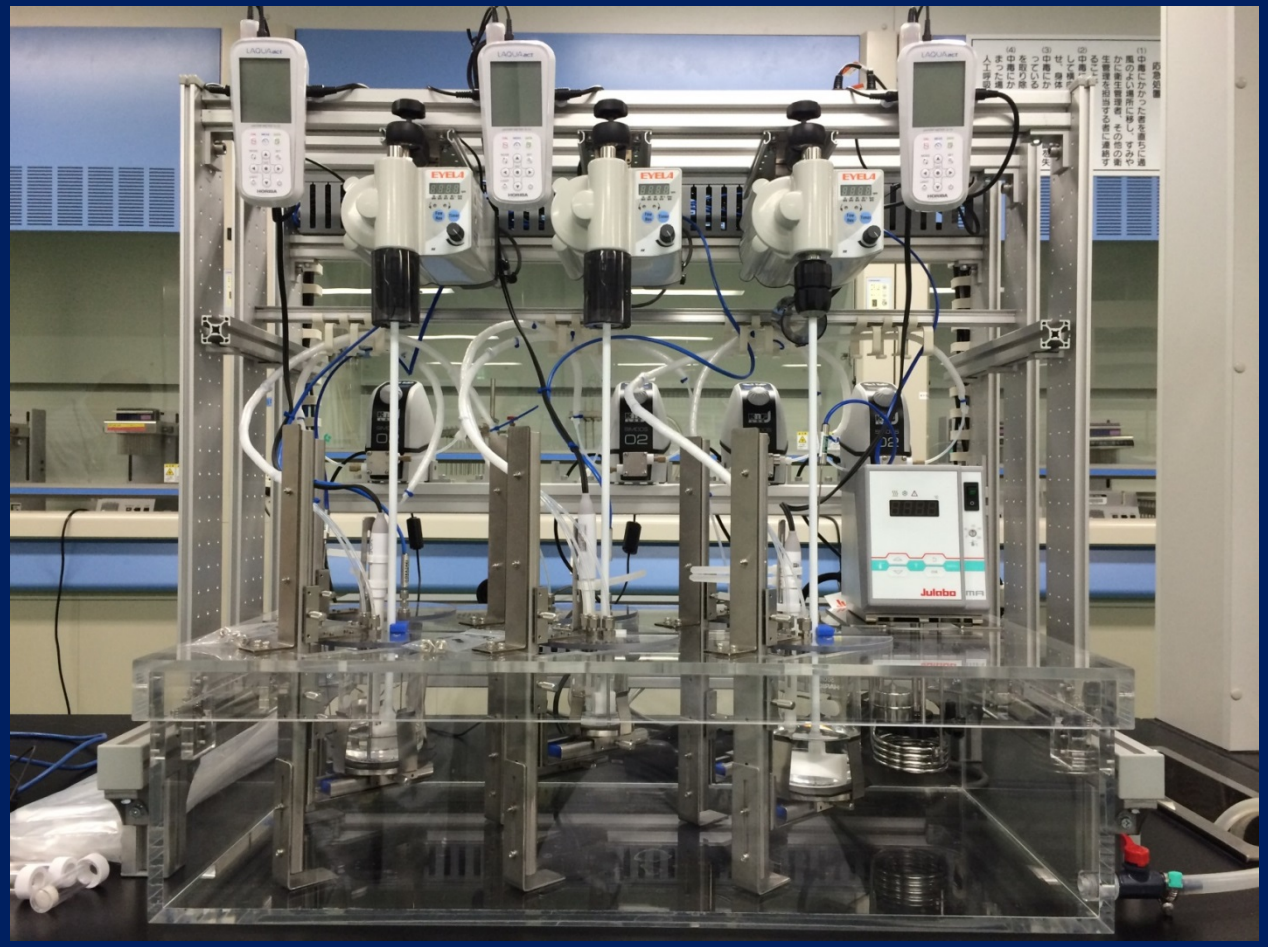
Pharmacokinetic

$$dC / dt = (dM / dt)1 / V$$
$$= k_a \cdot \Delta C \cong k_a \cdot C$$
$$k_a = 1 / \sec$$

$$k_a = (S / V) \cdot P_{eff}$$

Software e.g. GastroPlus®, SimCyp

Gastrointestinal Simulator (GIS)*



ASD=Artificial Stomach Duodenum

S. Takeuchi, (Sawai-Japan) personal communication)

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Raimar Loebenberg, Visiting Scientist
Jozef Al-Gousous, PostDoc
Arjang Talattof, Consultant
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John Duan – Pharmacologist
Hong Wen - Chemist
Dajun Sun – DQMM/ORS/OGD/CDER
Stephanie Choi – Acting Associate Director for Science
Monifa Coleman, Team Lead, Contracting Officer
Ronald Rouse, CO, Division Director

Colleagues and Associates
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Dr. Peter Langguth (JGU Mainz, DE)
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*Funding: FDA
HHSF223201510157C
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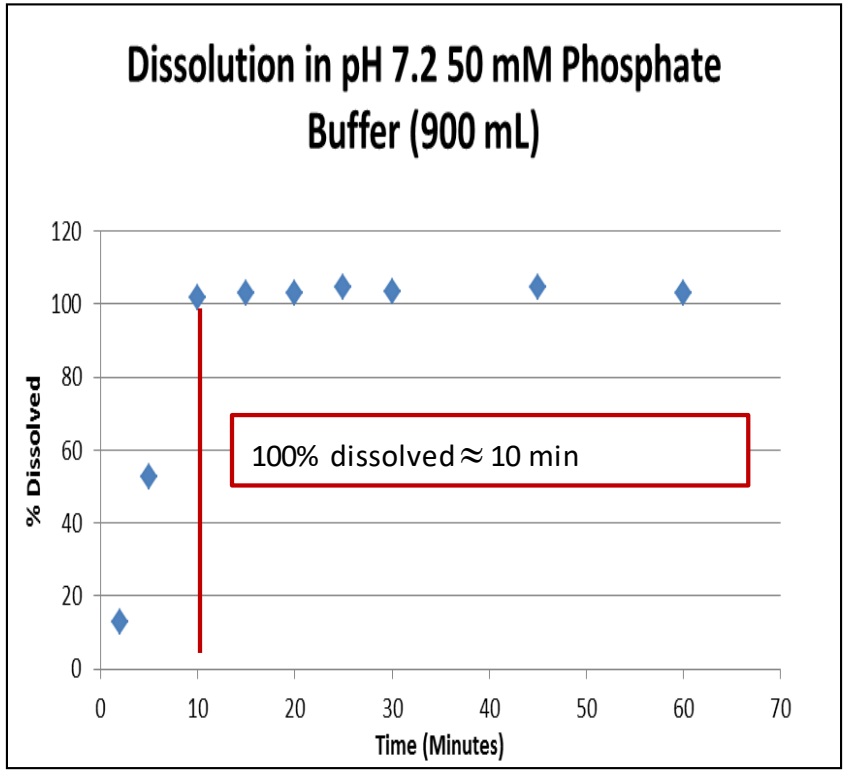

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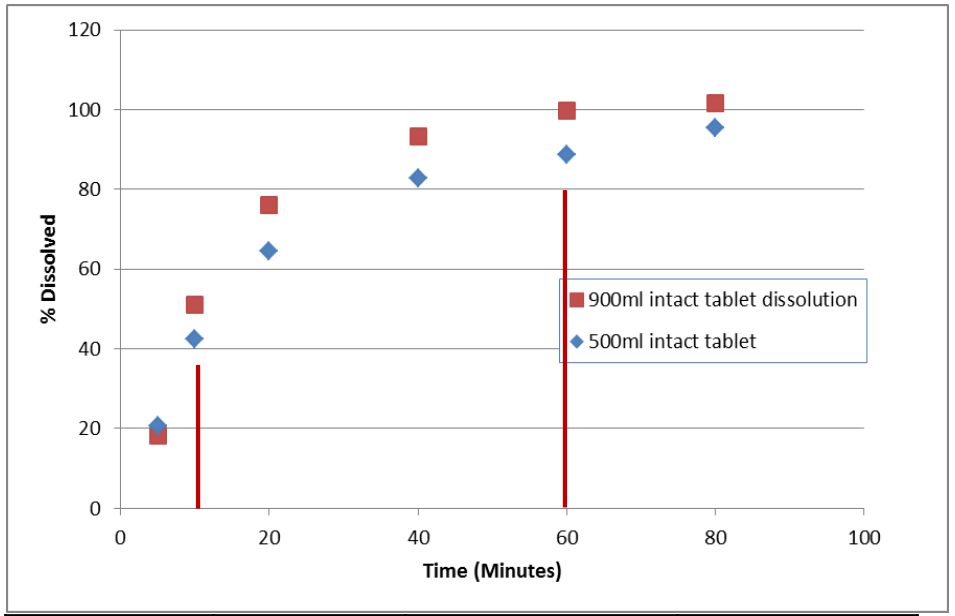

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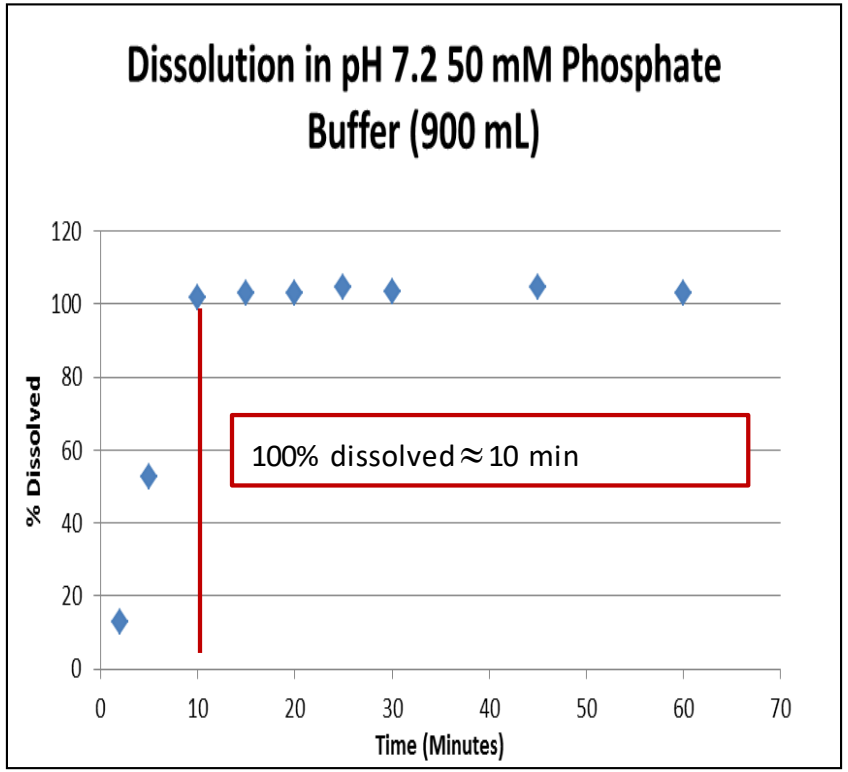

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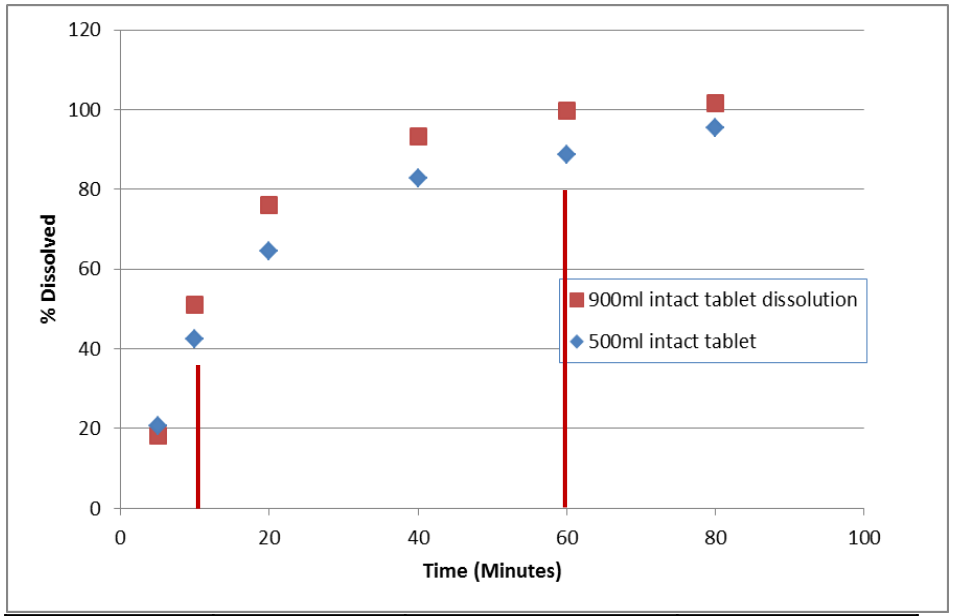

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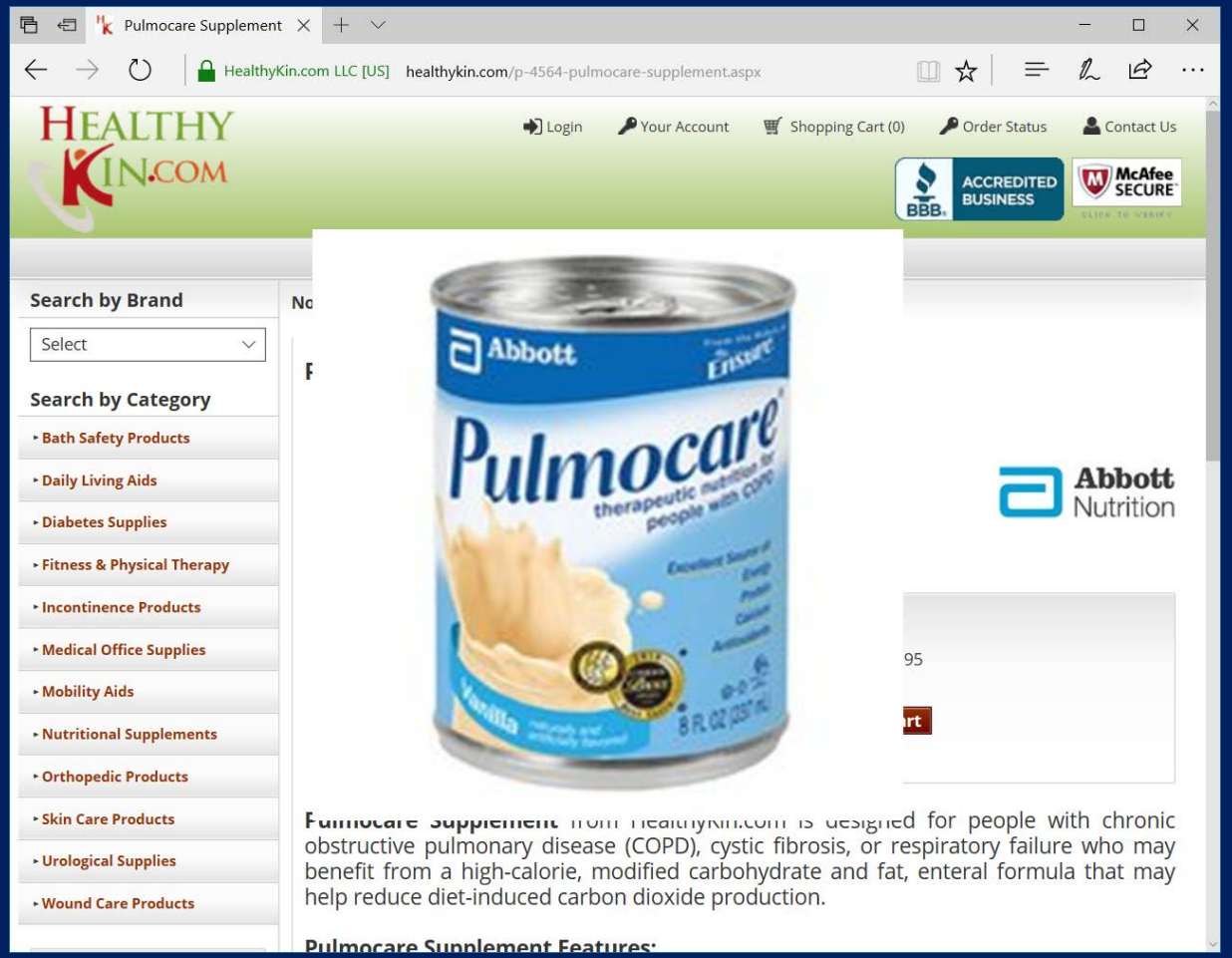
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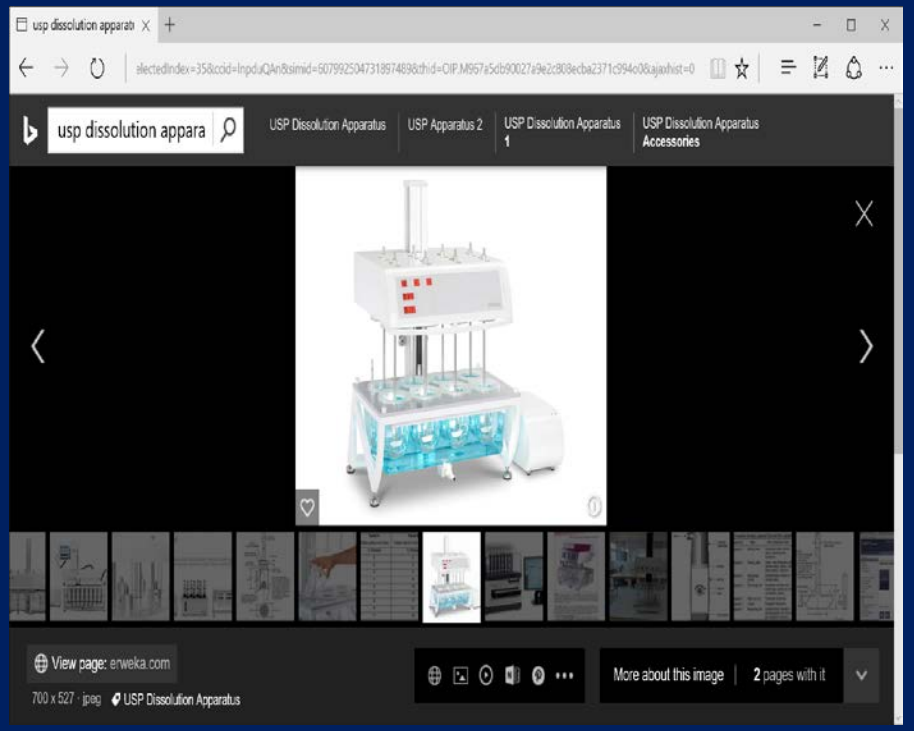
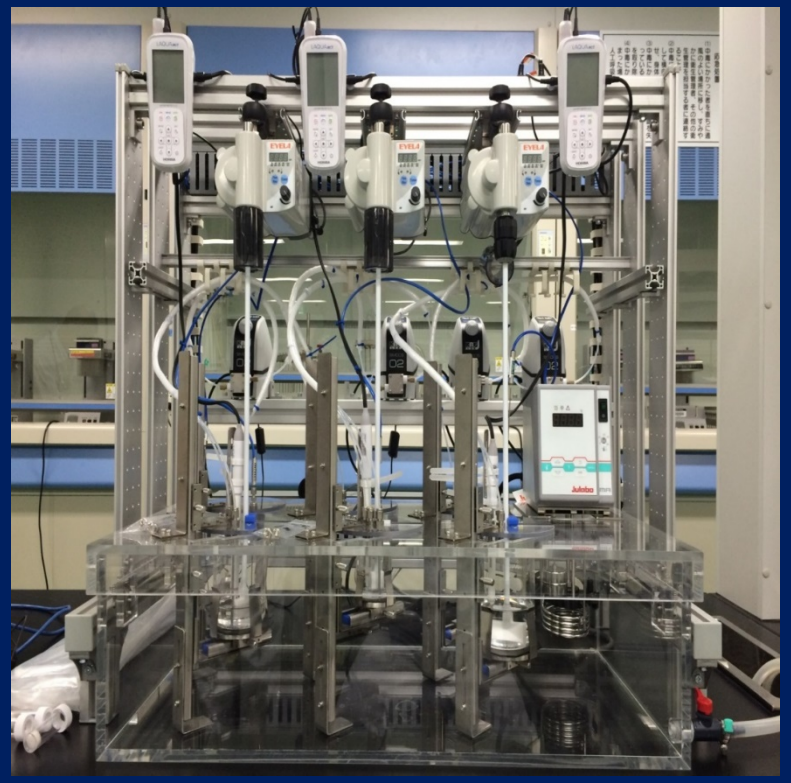
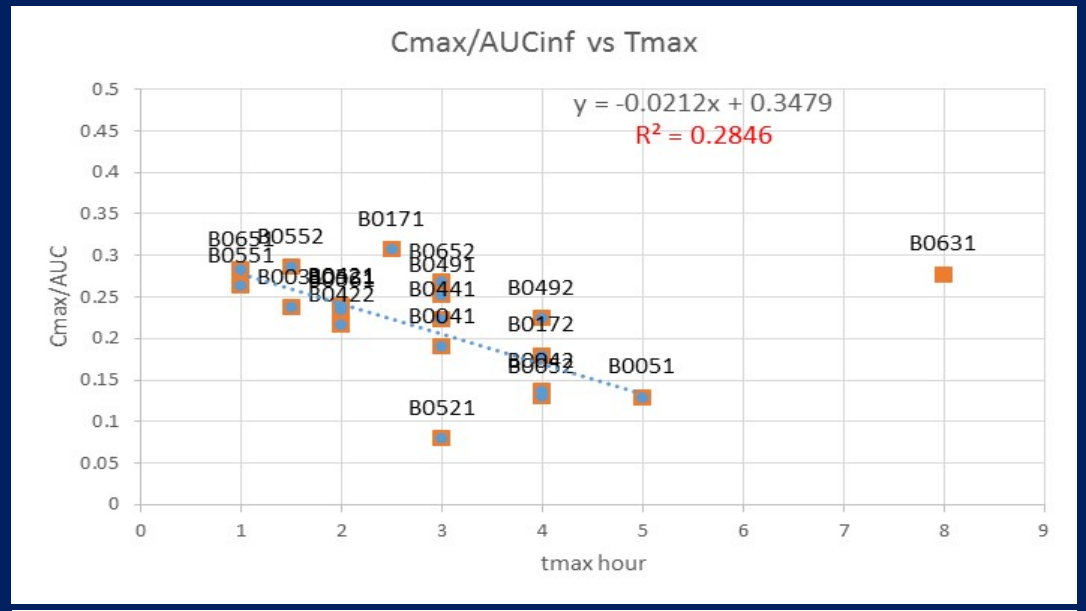
Login
Your Account
Shopping Cart (0)
Order Status
Contact Us
ACCREDITED BUSINESS
McAfee SECURE
Search by Brand
Select
Search by Category
Bath Safety Products
Daily Living Aids
Diabetes Supplies
Fitness & Physical Therapy
Incontinence Products
Medical Office Supplies
Mobility Aids
Nutritional Supplements
Orthopedic Products
Skin Care Products
Urological Supplies
Wound Care Products
Abbott
Ensure
Pulmocare
therapeutic nutrition for people with COPD
Vanilla
8 FL OZ (237 mL)
Abbott Nutrition
obstructive pulmonary disease (COPD), cystic fibrosis, or respiratory failure who may benefit from a high-calorie, modified carbohydrate and fat, enteral formula that may help reduce diet-induced carbon dioxide production.

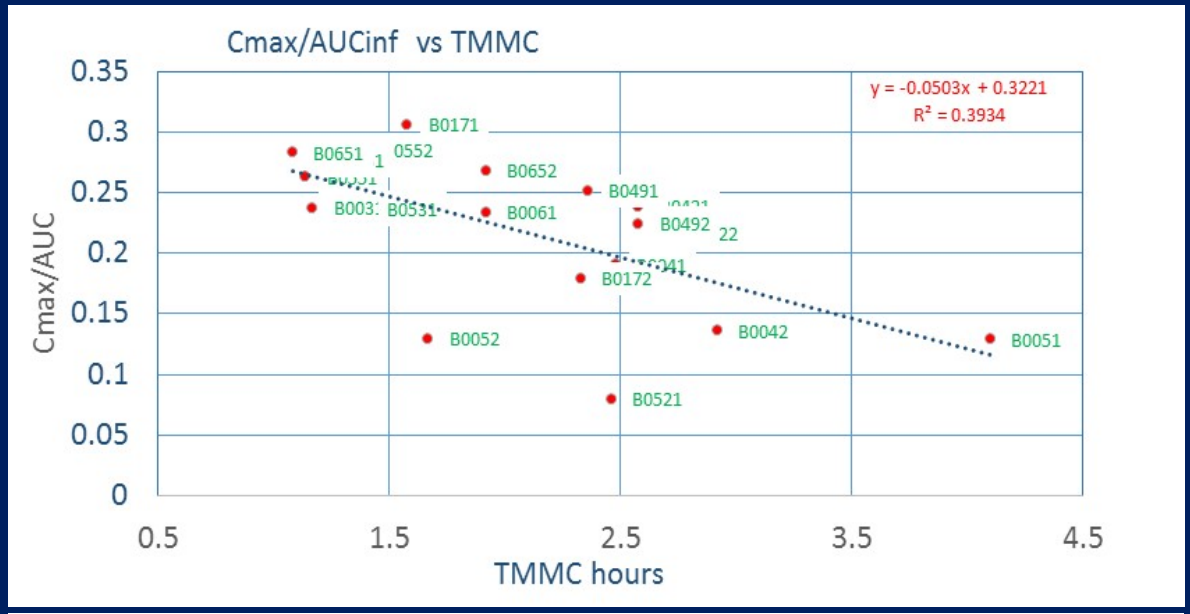
Transition to in vivo relevance

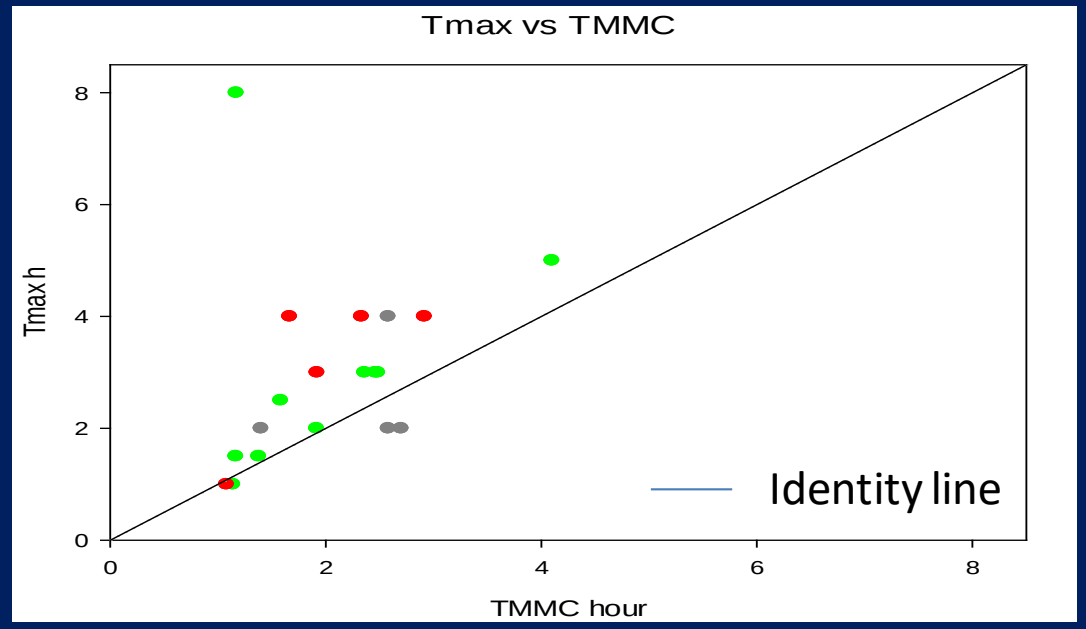


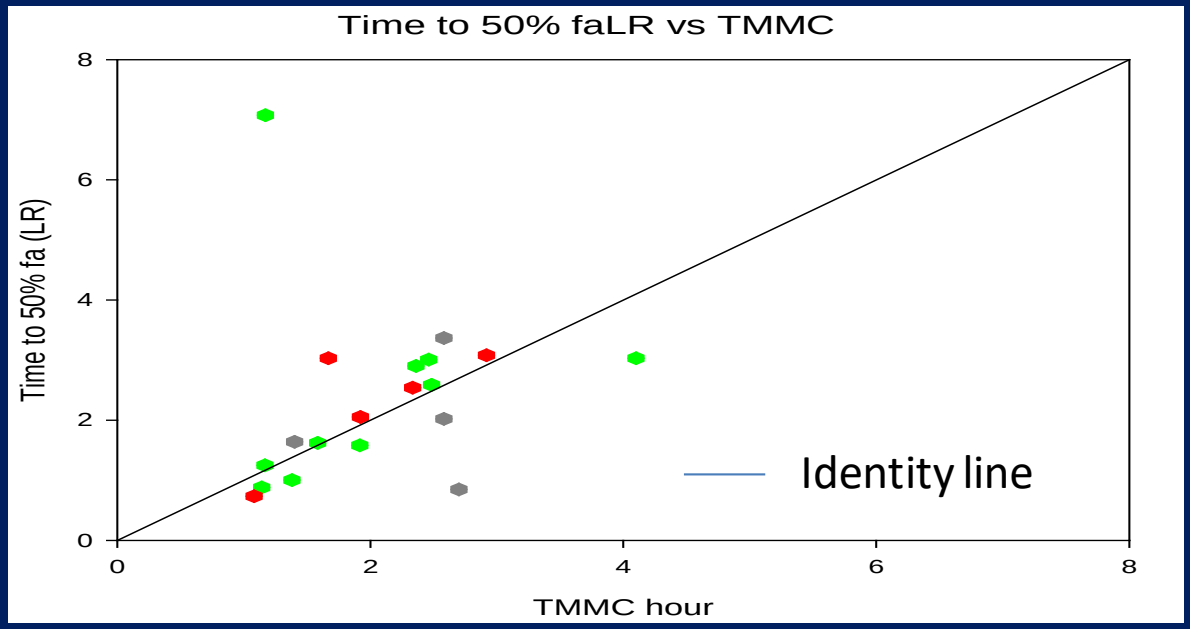


Exploratory data analysis: Link PK with GI motility, TIII – Post Dose Fasted state









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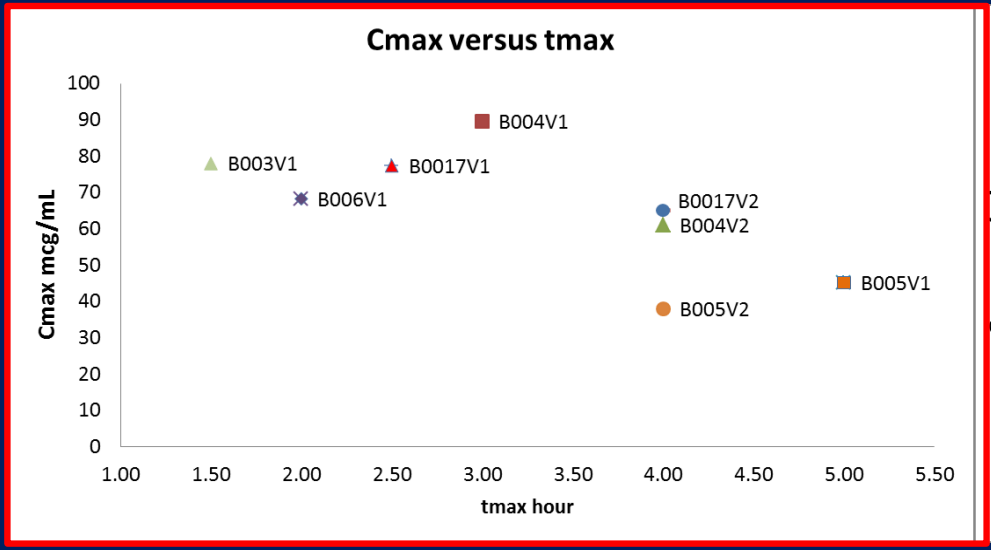
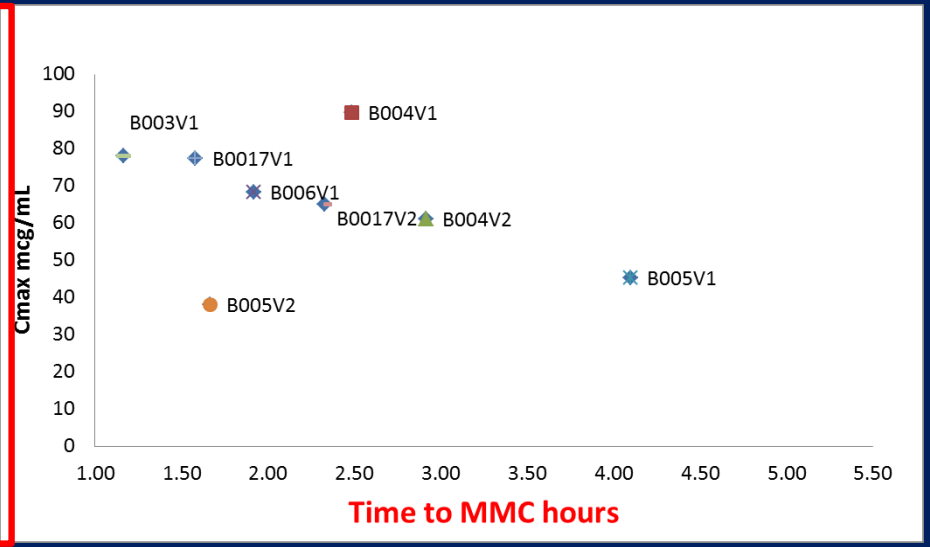
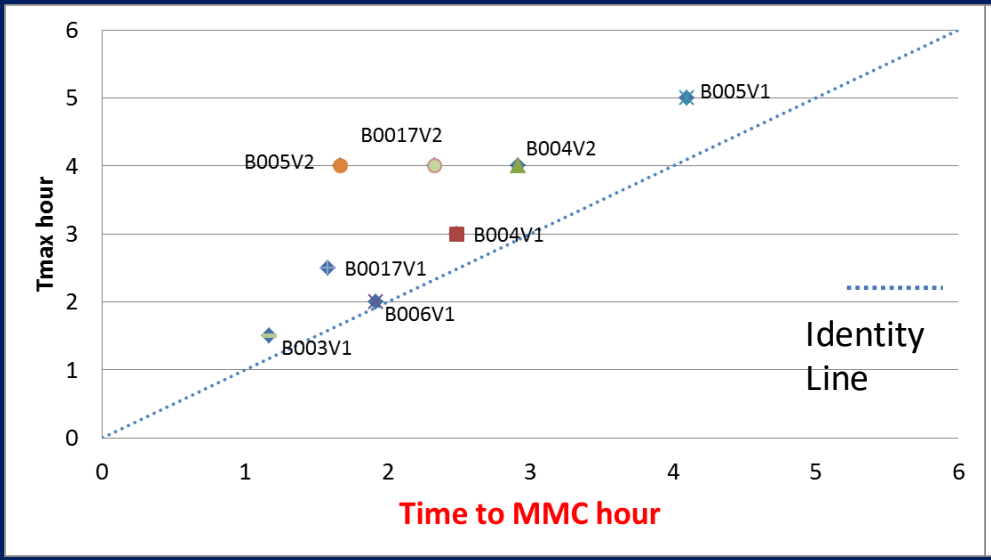
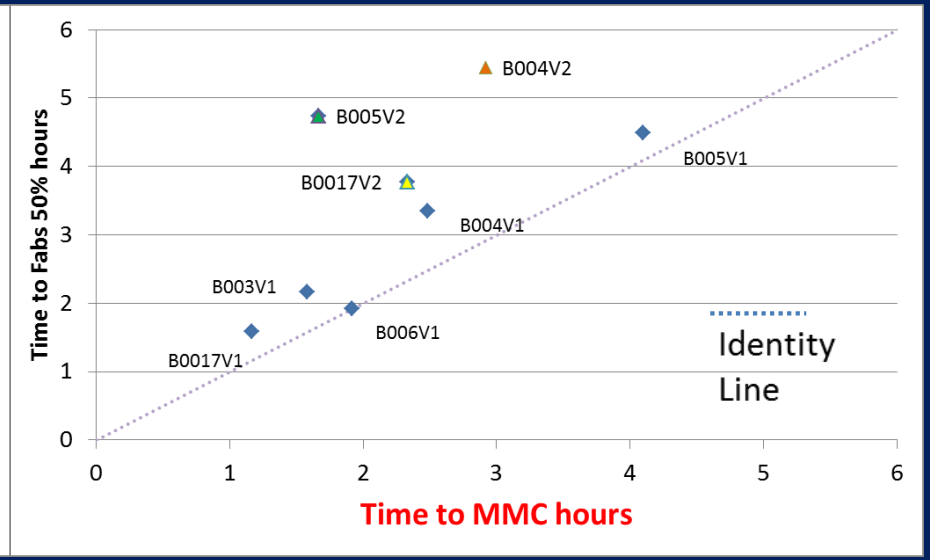


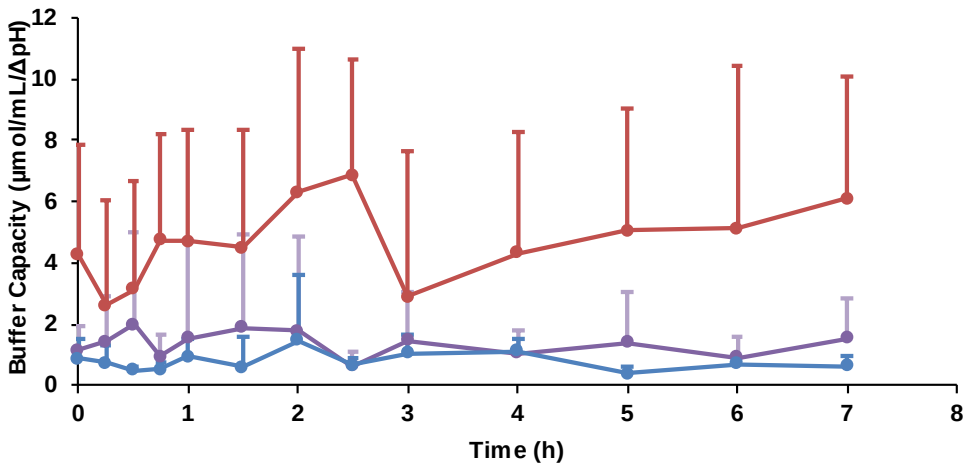




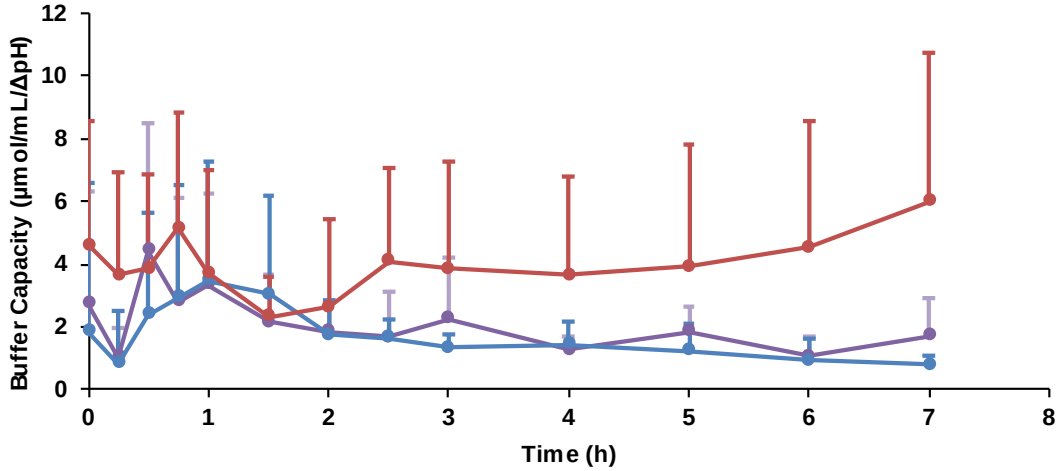


GI Buffer Capacity: Very Low

A: Fasted



B: Fed



Buffer Capacity Duodenum Buffer Capacity Jejunum Buffer Capacity Stomach

04/24/2017

Low Buffer Capacity Along The Human Gastrointestinal Tract: Implications for *in vivo* Dissolution and Absorption of Ionized Drugs

Bart Hens[1], Yasuhiro Tsume[1], Marival Bermejo[2], Joseph Dickens[3], Kerby Shedden[3], Niloufar Salehi[1], Bo Wen[1], Jeffrey Wysocki[1], Paulo Paixao[4], Raimar Loebenberg[5], Mark J. Koenigsknecht[1], Allen Lee[6], Jason R. Baker[6], William L. Hasler[6], Ann F. Fioritto[1], Greg Amidon[1], Alex Yu[1], Gail Benninghoff[1], Arjang Talattof[7], Robert Lionberger[8], Jianghong Fan[8], Duxin Sun[1], Gordon L. Amidon[1*]

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[7]Deloitte, Arlington, Virginia 22209, United States

[8]Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

Corresponding Author

* Prof. Dr. Gordon L. Amidon

GI Buffer Capacity

- Submitted to Mol Pharmaceutics
  - OrBiTo Special Issue
  - Largest Effort (in history) in Biopharmaceutical Sciences
- New Era in Oral Biopharmaceutics
- => Other Routes
- Physiological-Physical-Material at the site of Application

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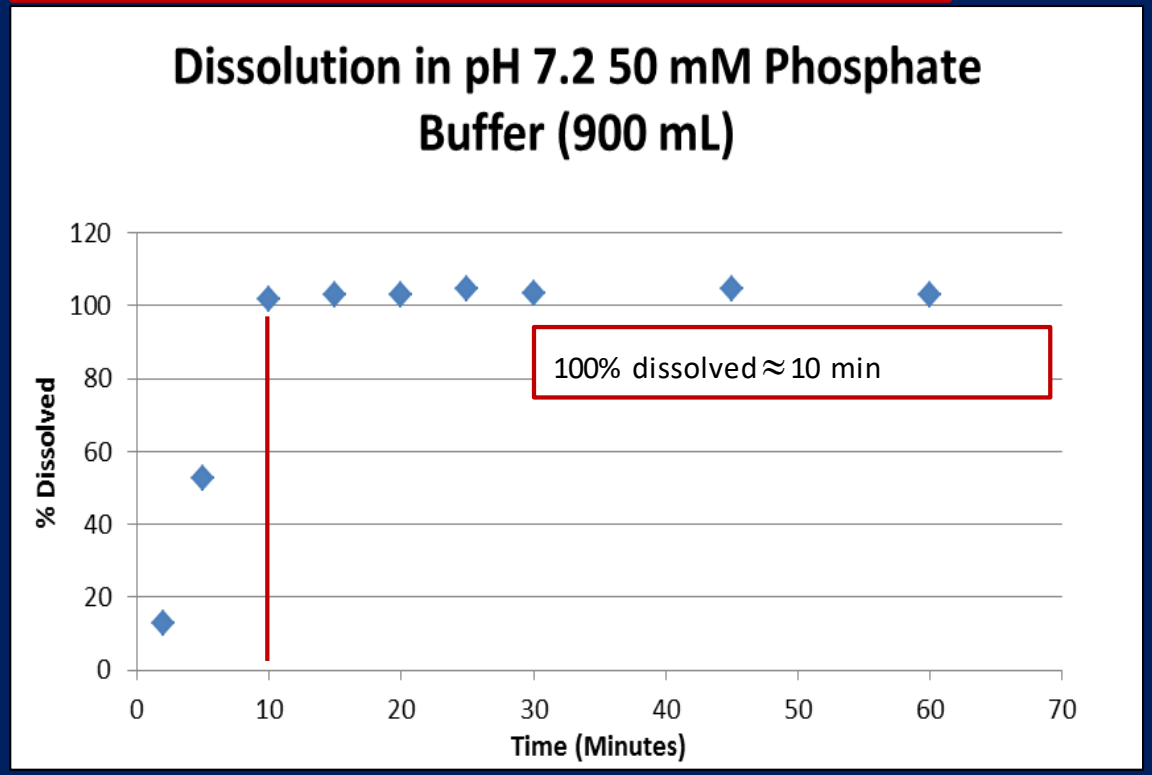

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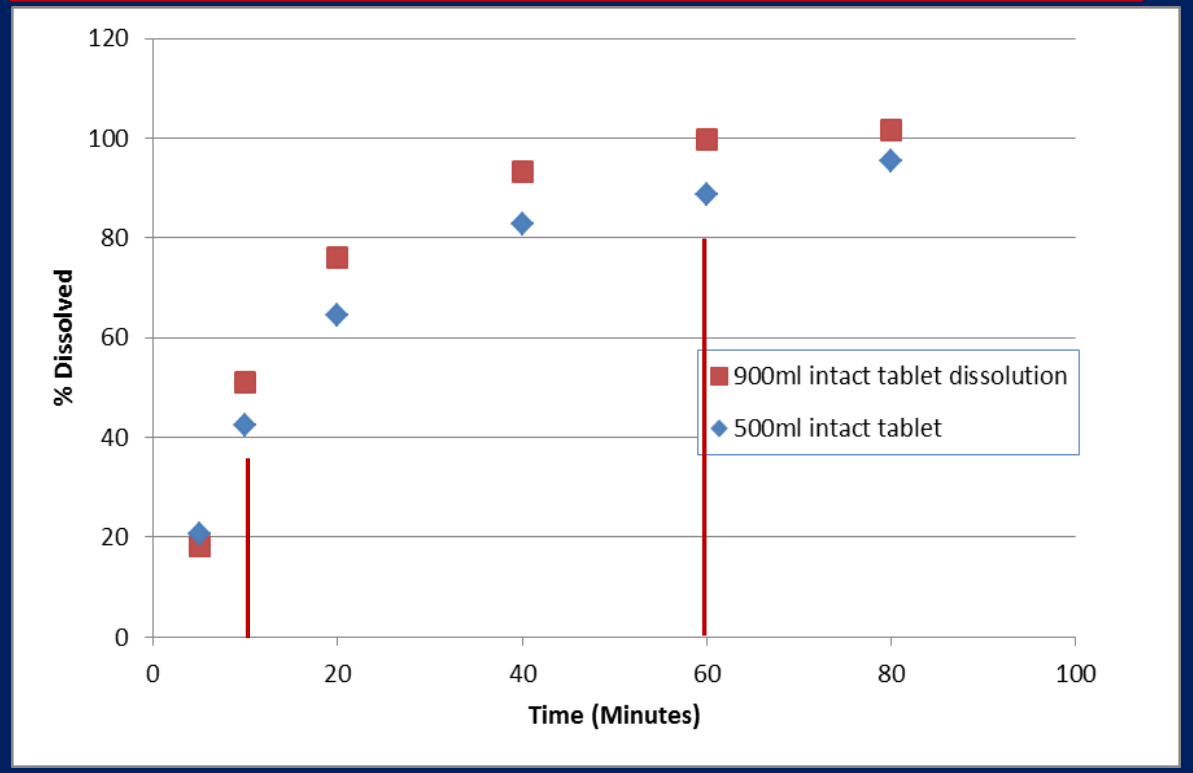

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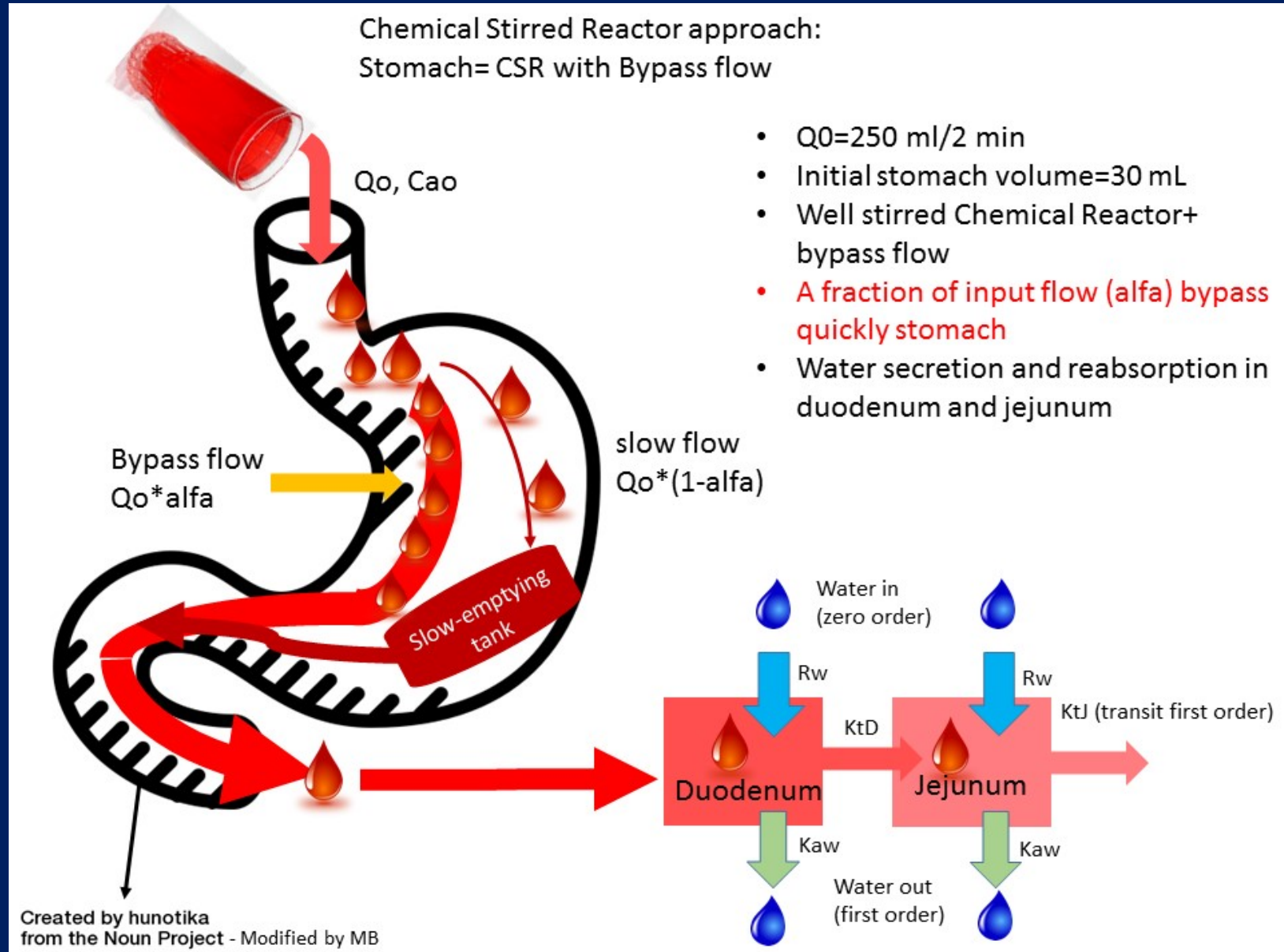
Chemical Stirred Reactor approach:
Stomach= CSR with Bypass flow

- Q0=250 ml/2 min
- Initial stomach volume=30 mL
- Well stirred Chemical Reactor+ bypass flow
- A fraction of input flow (alfa) bypass quickly stomach
- Water secretion and reabsorption in duodenum and jejunum



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from the Noun Project - Modified by MB

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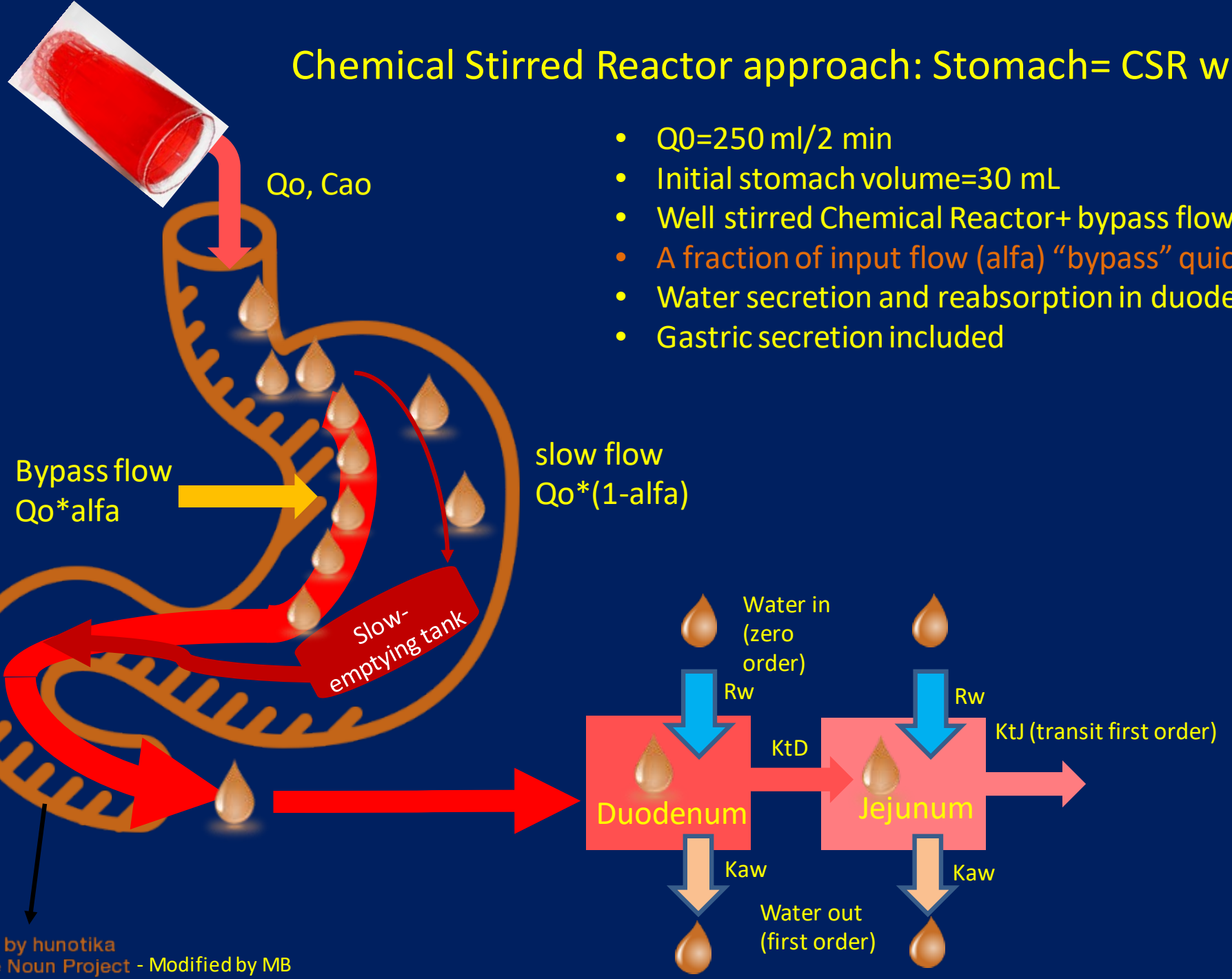

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molecular pharmaceutics

Article

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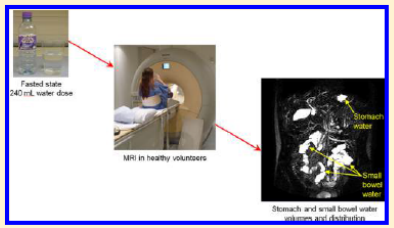
Supporting Information

ABSTRACT: The rate and extent of drug dissolution and absorption from solid oral dosage forms is highly dependent upon the volumes and distribution of gastric and small intestinal water. However, little is known about the time courses and distribution of water volumes *in vivo* in an undisturbed gut. Previous imaging studies offered a snapshot of water distribution in fasted humans and showed that water in the small intestine is distributed in small pockets. This study aimed to quantify the volume and number of water pockets in the upper gut of fasted healthy humans following ingestion of a glass of water (240 mL, as recommended for bioavailability/bioequivalence (BA/BE) studies), using recently validated noninvasive magnetic resonance imaging (MRI) methods. Twelve healthy volunteers underwent upper and lower abdominal MRI scans before drinking 240 mL (8 fluid ounces) of water. After ingesting the water, they were scanned at intervals for 2 h. The drink volume, inclusion criteria, and fasting conditions matched the international standards for BA/BE testing in healthy volunteers. The images were processed for gastric and intestinal total water volumes and for the number and volume of separate intestinal water pockets larger than 0.5 mL. The fasted stomach contained 35 ± 7 mL (mean ± SEM) of resting water. Upon drinking, the gastric fluid rose to 242 ± 9 mL. The gastric water volume declined rapidly after that with a half emptying time ($T_{50\%}$) of 13 ± 1 min. The mean gastric volume returned back to baseline 45 min after the drink. The fasted small bowel contained a total volume of 43 ± 14 mL of resting water. Twelve minutes after ingestion of water, small bowel water content rose to a maximum value of 94 ± 24 mL contained within 15 ± 2 pockets of 6 ± 2 mL each. At 45 min, when the glass of water had emptied completely from the stomach, total intestinal water volume was 77 ± 15 mL distributed into 16 ± 3 pockets of 5 ± 1 mL each. MRI provided unprecedented insights into the time course, number, volume, and location of water pockets in the stomach and small intestine under conditions that represent standard BA/BE studies using validated techniques. These data add to our current understanding of gastrointestinal physiology and will help improve physiological relevance of *in vitro* testing methods and *in silico* transport analyses for prediction of bioperformance of oral solid dosage forms, particularly for low solubility Biopharmaceutics Classification System (BCS) Class 2 and Class 4 compounds.

KEYWORDS: *gastric emptying, intestinal water, bioperformance, dissolution, small bowel, MRI*



Molecular Pharmaceutics — Article

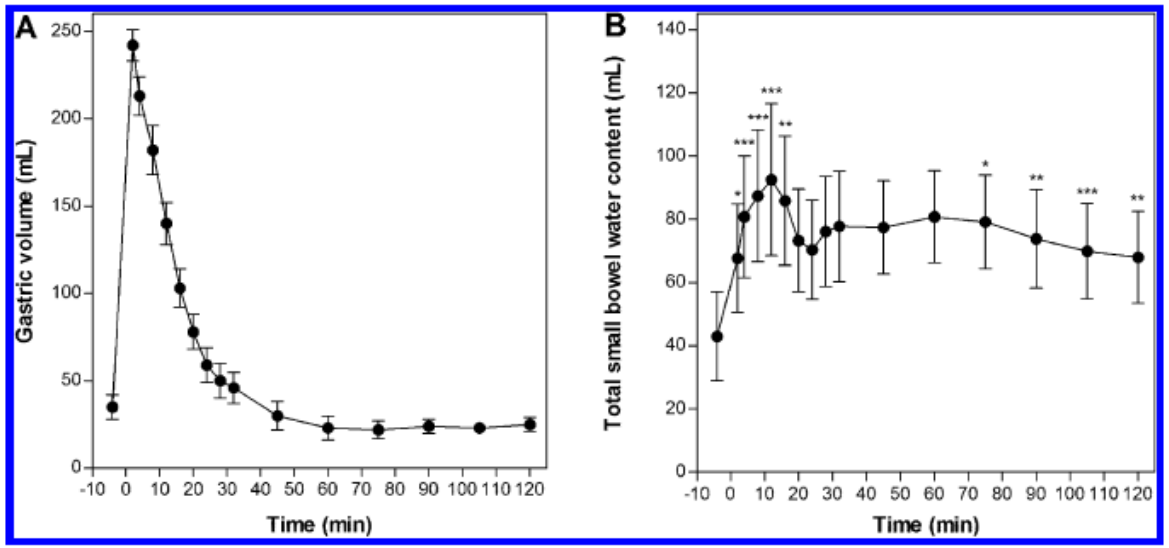


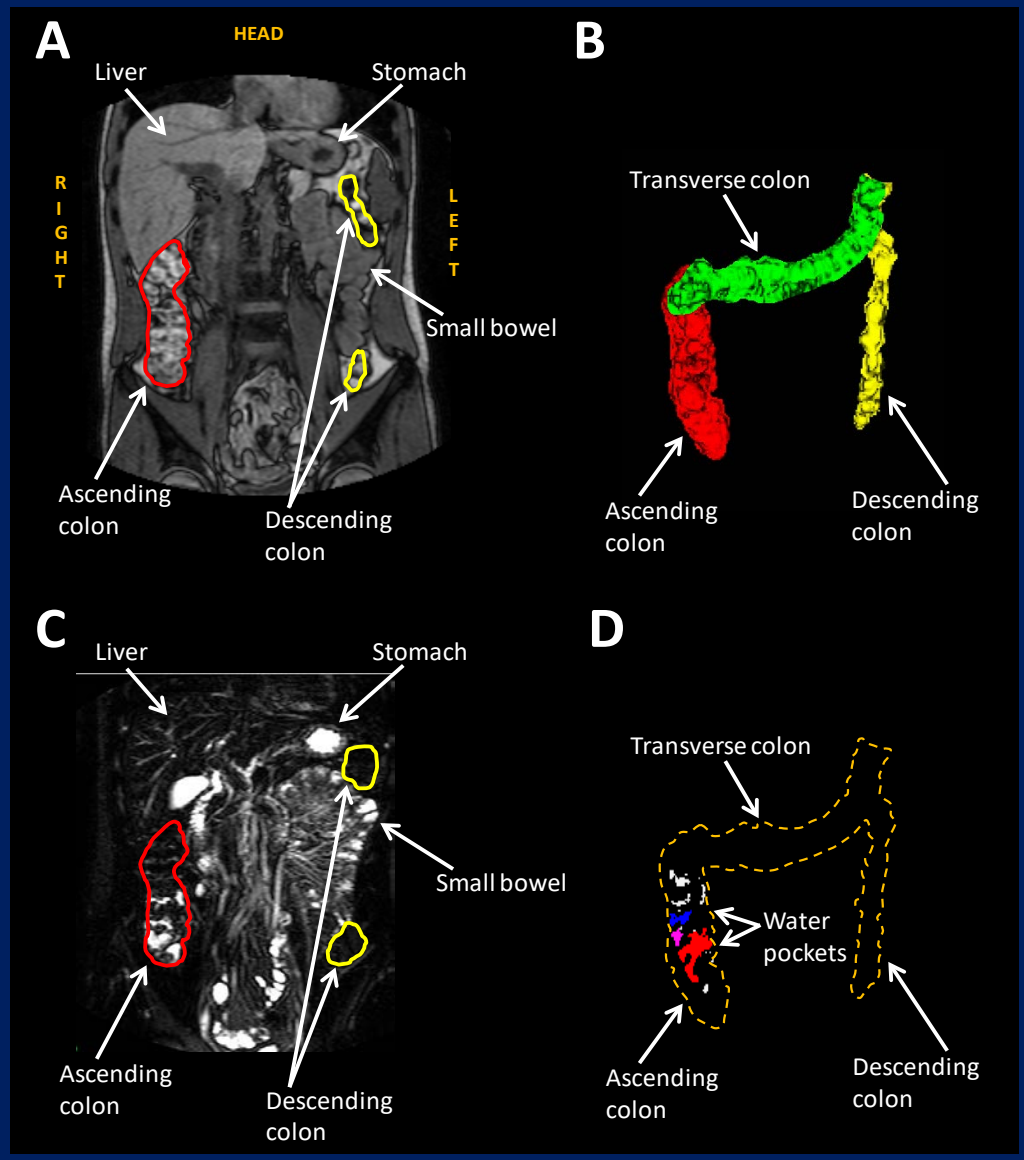
Figure 2. (A) Mean gastric volume and (B) mean total small bowel water content before and after ingestion of a 240 mL dose of water given at $t = 0$ min. $n = 12$ healthy volunteers. Error bars represent ± SEM. Dunn's multiple comparison test versus baseline value * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Error bars represent ± SEM.

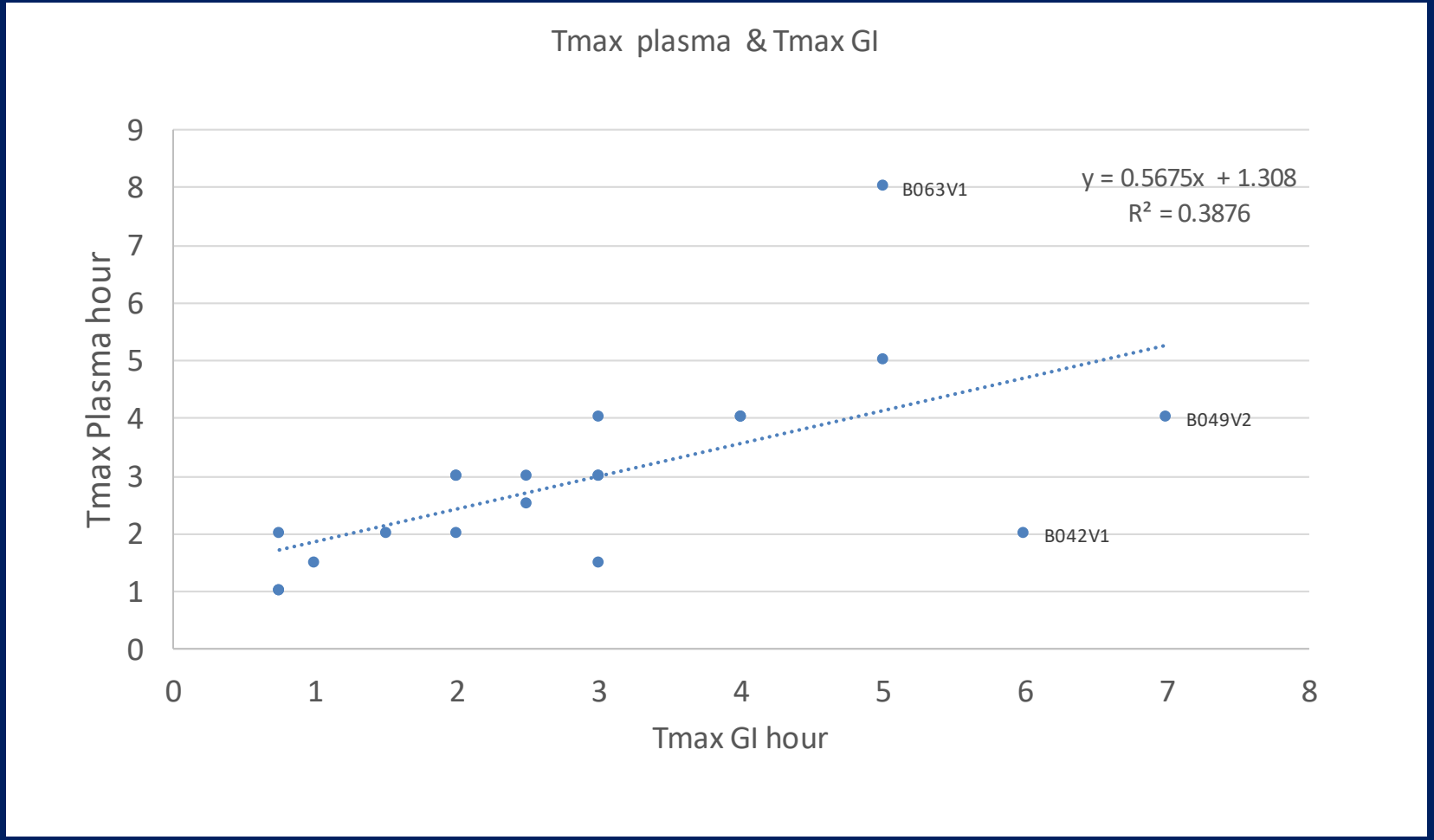
Mean Gastric volume

Small bowel water content

MRI GI Fluid Study

(Where we are Going)





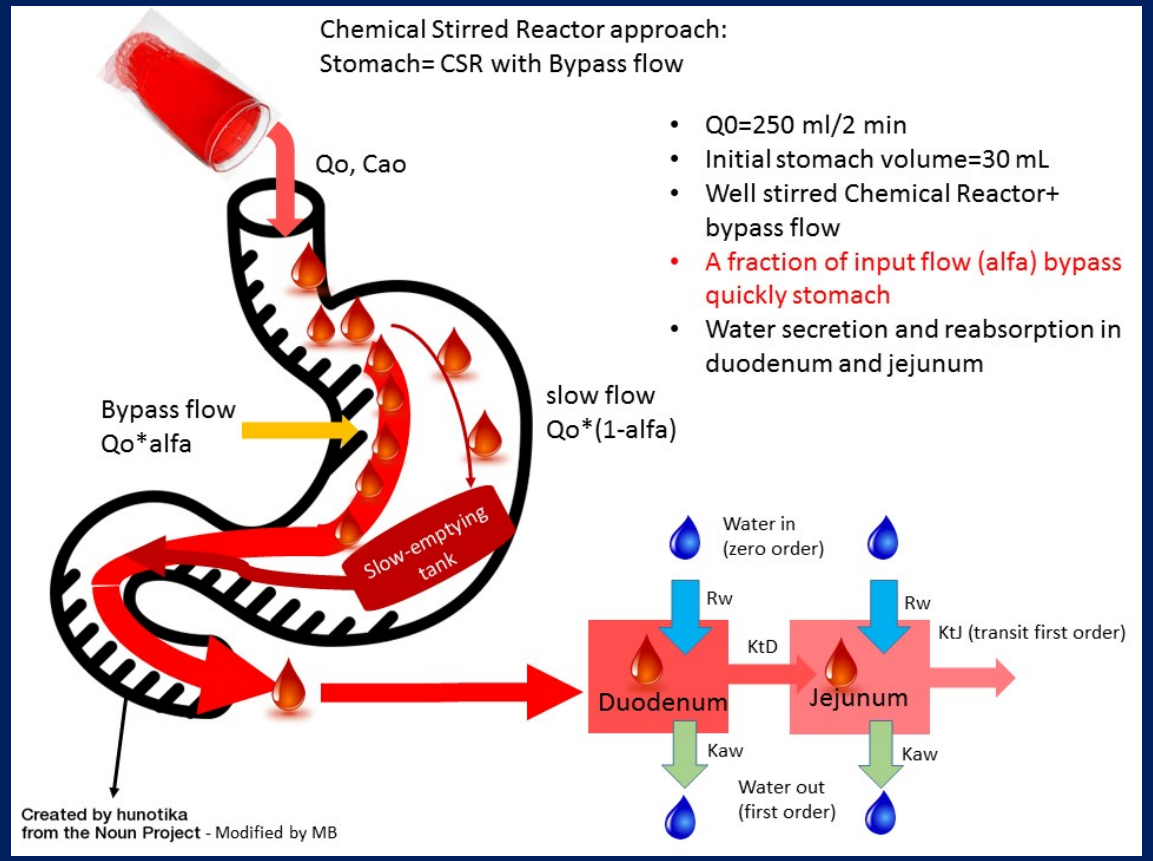
Correlation between plasma tmax and the time of maximal Ibuprofen concentration in Duodenum+Jejunum

USP Buffer Capacity

Table 4: Osmolarity, ionic strength and buffer capacity of the two buffers

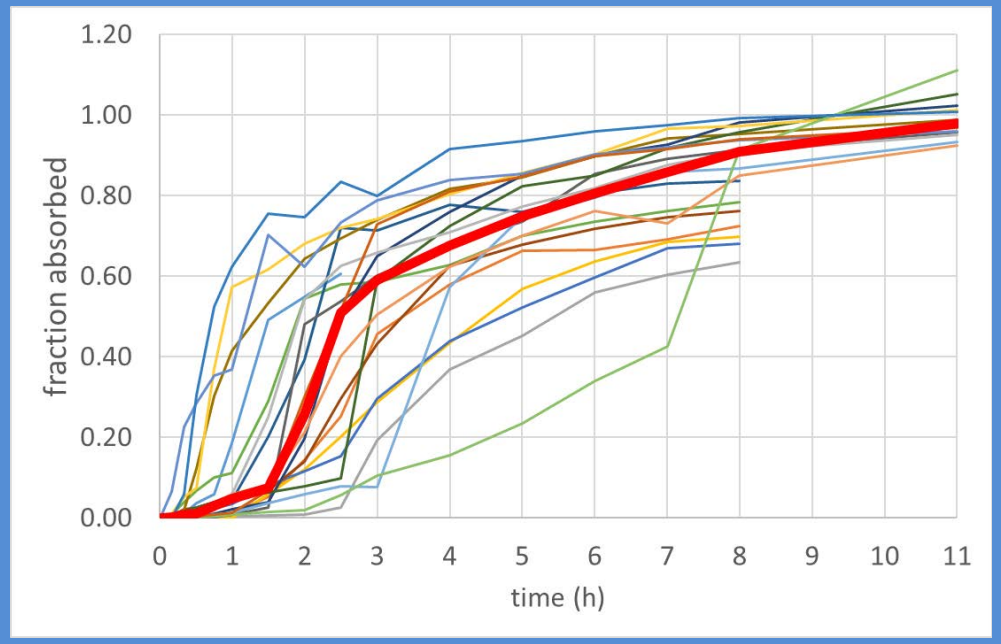
Medium	Osmolarity [mOsmol/kg]	Ionic strength [mol/L]	Buffer capacity [mEq/L/pH unit]
Simulated Intestinal Fluid, pH 6.8 (SIFsp); USP 26	113	0.0720	18.4±0.2
Phosphate Standard Buffer pH 6.8 (IntPh 3)	115	0.0753	18.6±0.1

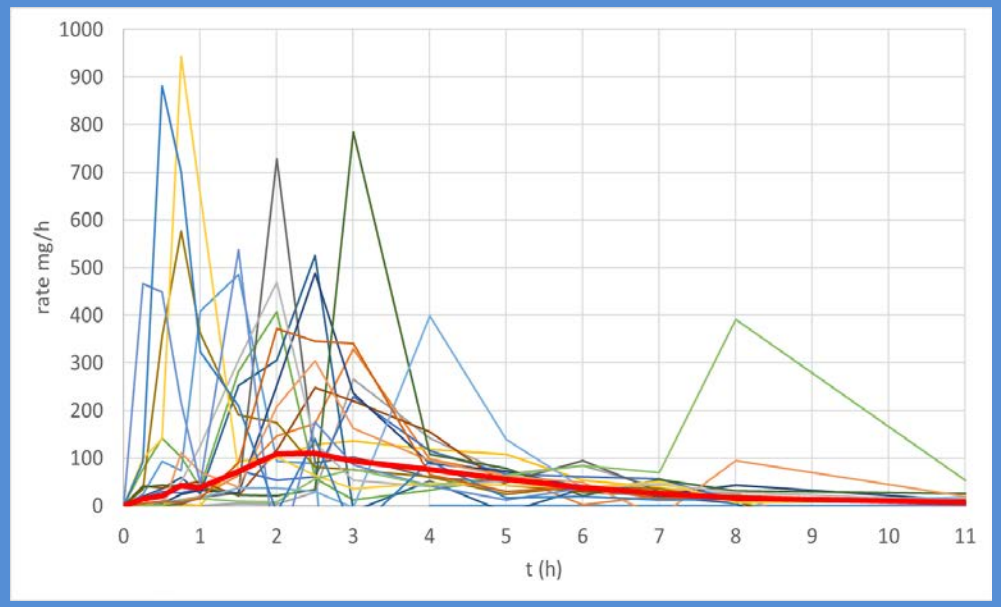
Goal: Measure GI and Plasma under BE Conditions



- Hypothesis:
- Major Cmax, AUC Variation is due to GI variation
  - In vivo Dissolution/Absorption Rate
  - Motility Variation
  - Random dosing (Fasted/Fed)
  - 1st-Pass Metabolism
    - Hepatic Linear
    - GI Non Linear dosage form Transit dependent

Plasma Levels and $F_{abs}(t)$ Ibuprofen

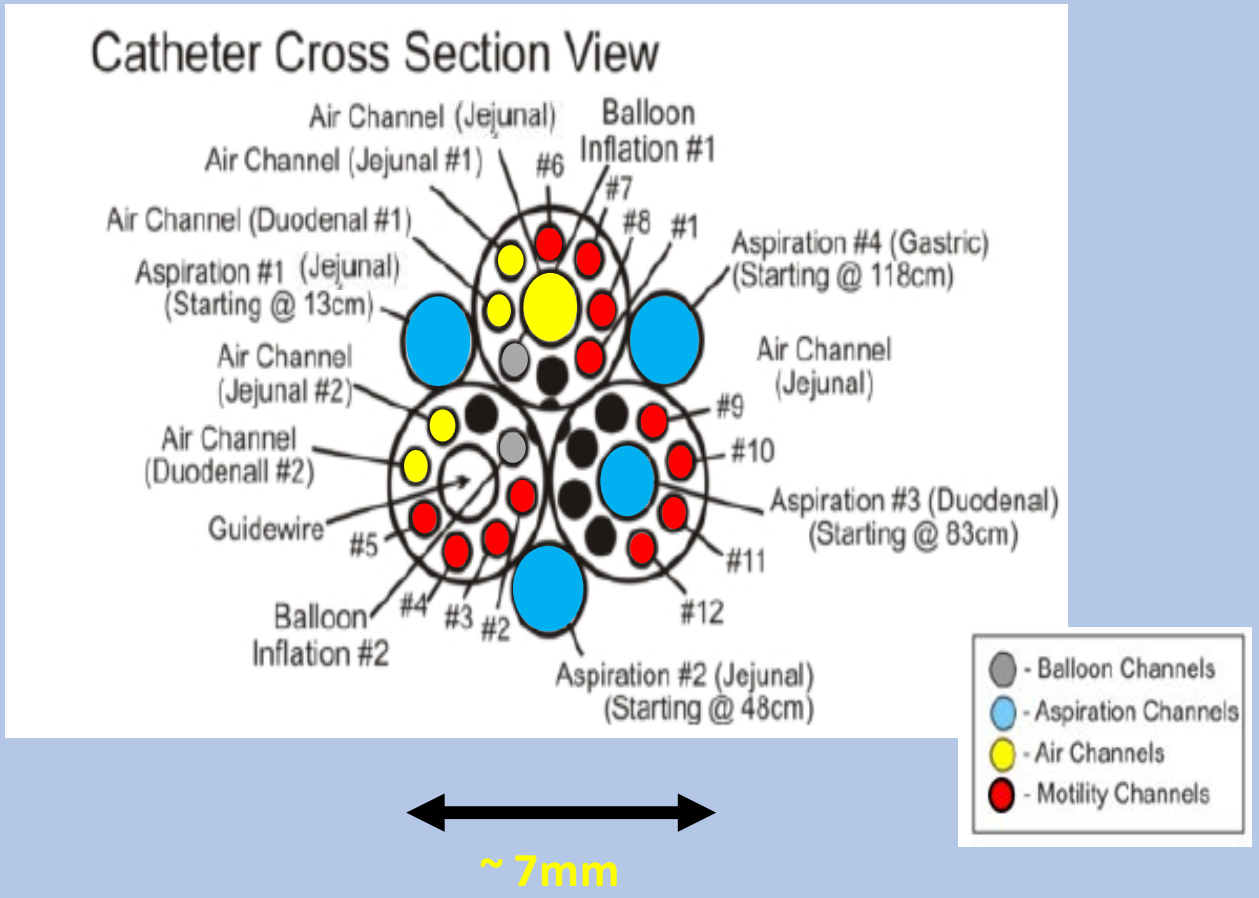




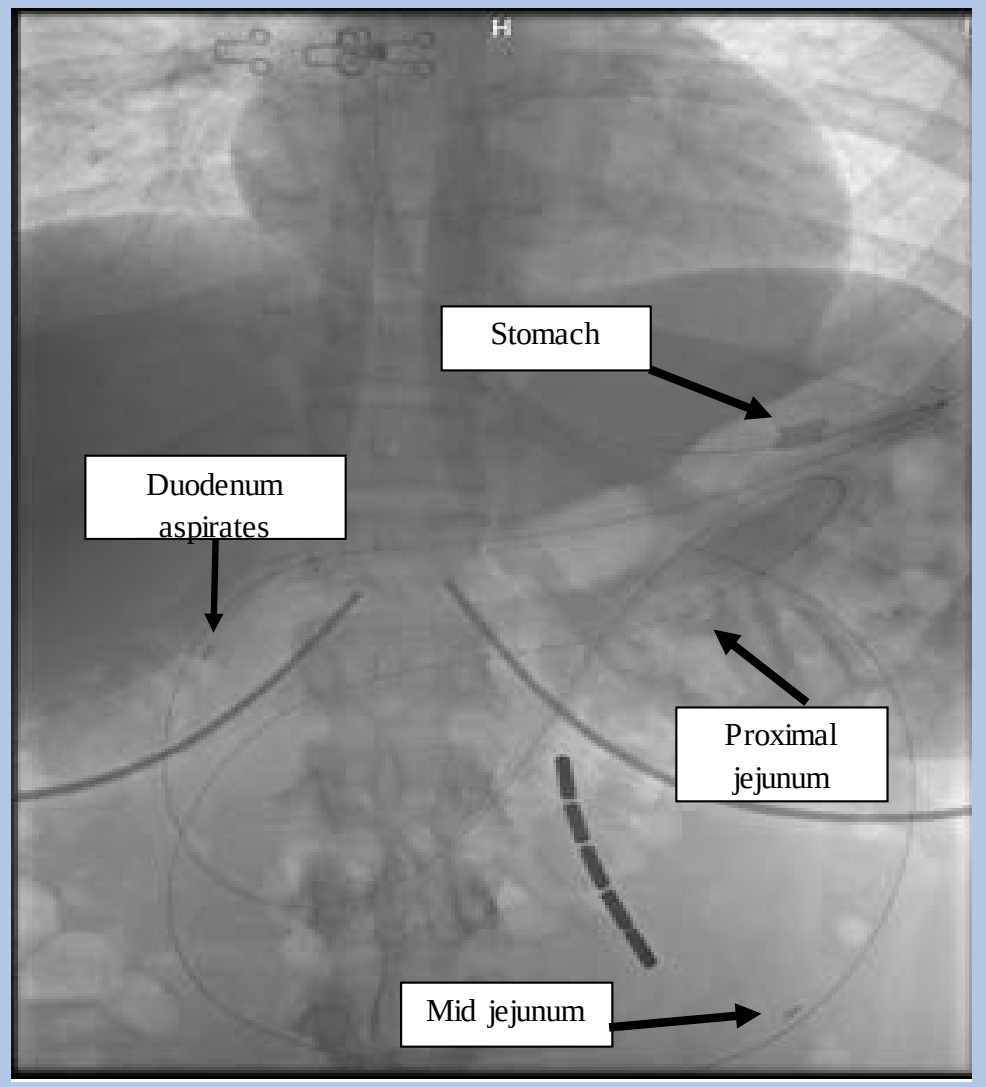
Subject	time to 50% fa (h)
B003V1	1.58
B004V1	3.35
B004V2	5.45
B005V1	4.49
B005V2	4.73
B006V1	1.92
B0017V1	2.16
B0017V2	3.35
B042V1	2.17
B042V2	1.36
B44V1	2.50
B049V1	2.91
B049V2	3.85
B052V1	2.98
B053V1	1.93
B055V1	0.91
B055V2	1.20
B063V1	8.43
B065V1	0.72
B065V2	2.46
average	2.92
median	2.48
max	8.43
min	0.72

Measuring GI Variables

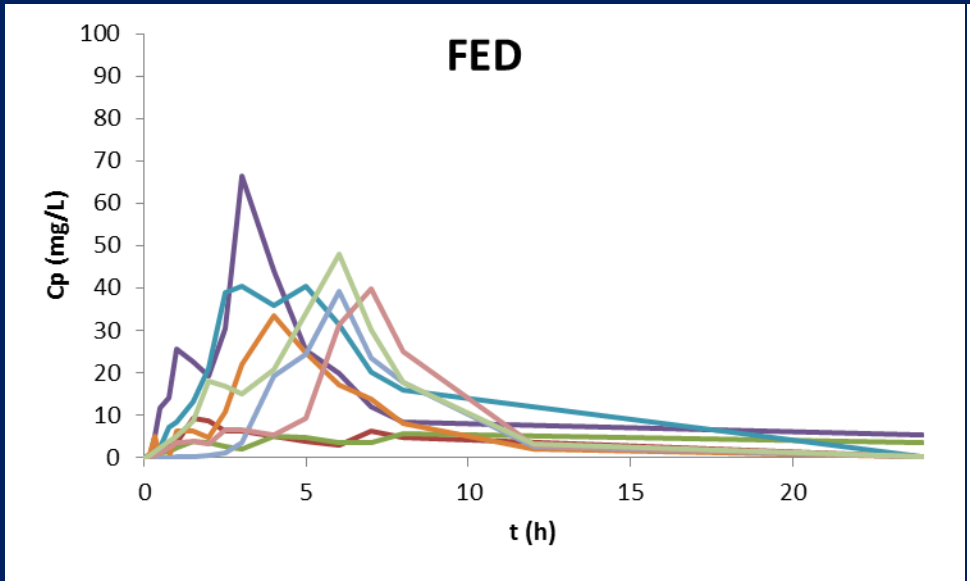
Tube Placement

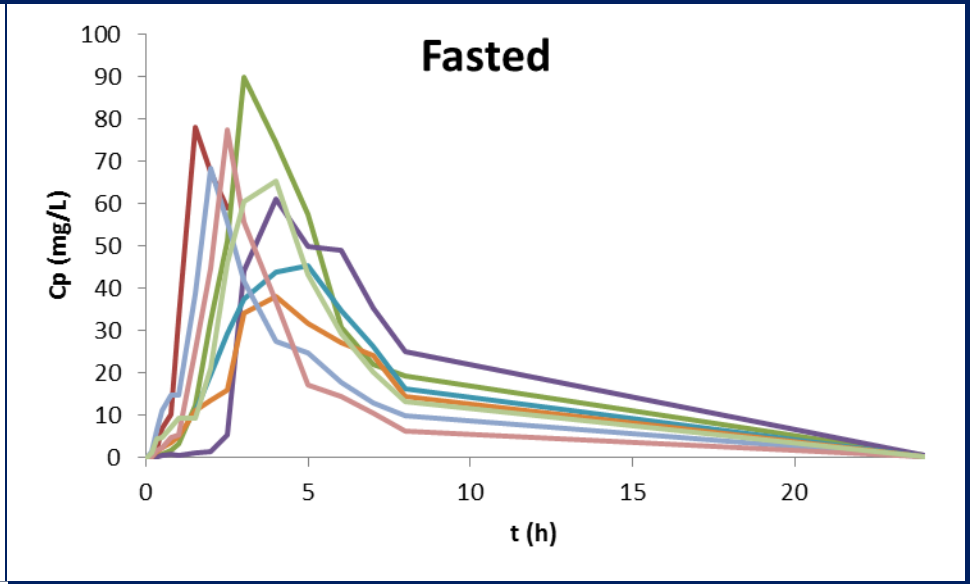


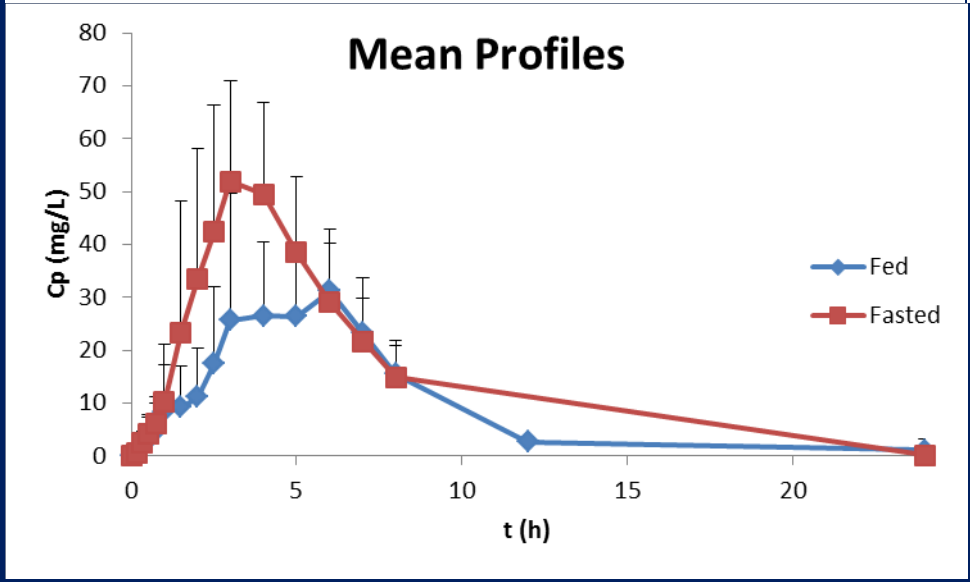
Fluoroscopy



Fed vs Fasted

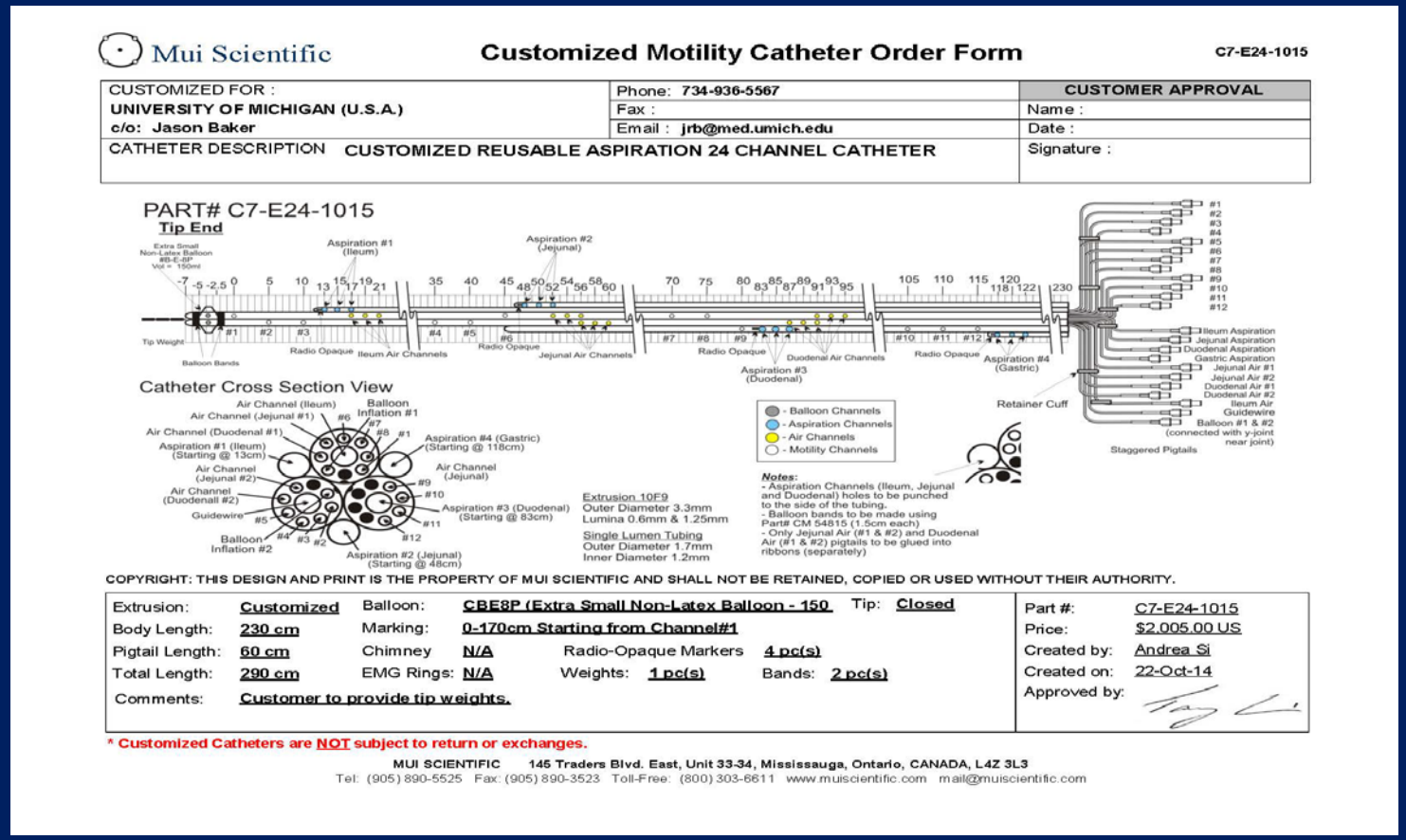






	Cmax*		Tmax		AUC*	
	fasted	fed	fasted	fed	fasted	fed
1	77	9	2.50	1.50	252	63
2	65	6	4.00	8.00	363	99
3	78	66	1.50	3.00	104	314
4	90	41	3.00	3.00	469	269
5	61	33	4.00	4.00	448	151
6	45	39	5.00	6.00	351	158
7	38	40	4.00	7.00	294	162
8	68	48	2.00	6.00	292	224
Mean	65	45	3.25	4.81	321	213
Fed/Fasted	0.68		1.48		0.66	
* - first 2 Fed Cases removed						

Catheter Design



Mui Scientific

Customized Motility Catheter Order Form

C7-E24-1015

CUSTOMIZED FOR :	Phone: 734-936-5567	CUSTOMER APPROVAL
UNIVERSITY OF MICHIGAN (U.S.A.)	Fax :	Name :
c/o: Jason Baker	Email : jrb@med.umich.edu	Date :
CATHETER DESCRIPTION CUSTOMIZED REUSABLE ASPIRATION 24 CHANNEL CATHETER		Signature :

PART# C7-E24-1015

Tip End

Aspiration #1 (Ileum)

Aspiration #2 (Jejunal)

Tip Weight

Balloon Bands

Radio Opaque

Ileum Air Channels

Jejunal Air Channels

Duodenal Air Channels

Aspiration #3 (Duodenal)

Aspiration #4 (Gastric)

Retainer Cuff

Staggered Pigtails

Ileum Aspiration
Jejunal Aspiration
Duodenal Aspiration
Gastric Aspiration
Jejunal Air #1
Jejunal Air #2
Duodenal Air #1
Duodenal Air #2
Ileum Air
Guidewire
Balloon #1 & #2 (connected with y-joint near joint)

Catheter Cross Section View

Air Channel (Ileum)
Balloon Inflation #1
Air Channel (Jejunal #1)
Air Channel (Duodenal #1)
Aspiration #1 (Ileum) (Starting @ 13cm)
Aspiration #4 (Gastric) (Starting @ 118cm)
Air Channel (Jejunal #2)
Air Channel (Jejunal)
Air Channel (Duodenal #2)
Guidewire
Aspiration #3 (Duodenal) (Starting @ 83cm)
Balloon Inflation #2
Aspiration #2 (Jejunal) (Starting @ 48cm)

- Balloon Channels
- Aspiration Channels
- Air Channels
- Motility Channels

Extrusion 10F9
Outer Diameter 3.3mm
Lumina 0.6mm & 1.25mm

Single Lumen Tubing
Outer Diameter 1.7mm
Inner Diameter 1.2mm

Notes:
- Aspiration Channels (Ileum, Jejunal and Duodenal) holes to be punched to the side of the tubing.
- Balloon bands to be made using Part# CM 54815 (1.5cm each)
- Only Jejunal Air (#1 & #2) and Duodenal Air (#1 & #2) pigtails to be glued into ribbons (separately)

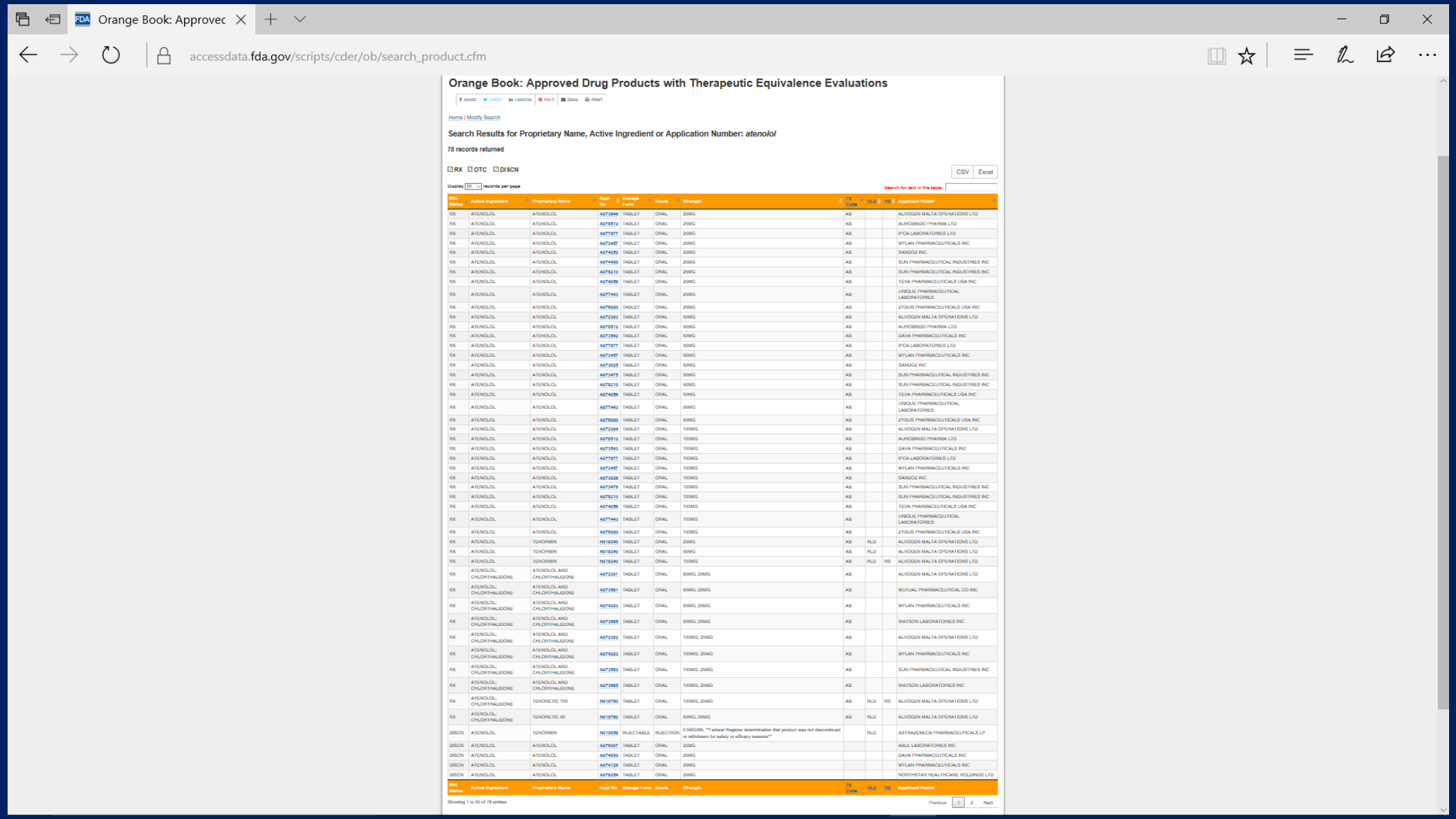
Extrusion:	Customized	Balloon:	CBE8P (Extra Small Non-Latex Balloon - 150	Tip:	Closed	Part #:	C7-E24-1015
Body Length:	230 cm	Marking:	0-170cm Starting from Channel#1			Price:	$2,005.00 US
Pigtail Length:	60 cm	Chimney	N/A	Radio-Opaque Markers	4 pc(s)	Created by:	Andrea Si
Total Length:	290 cm	EMG Rings:	N/A	Weights: 1 pc(s)	Bands: 2 pc(s)	Created on:	22-Oct-14
Comments:	Customer to provide tip weights.					Approved by:	

* Customized Catheters are NOT subject to return or exchanges.

MUI SCIENTIFIC 145 Traders Blvd. East, Unit 33-34, Mississauga, Ontario, CANADA, L4Z 3L3
Tel: (905) 890-5525 Fax: (905) 890-3523 Toll-Free: (800) 303-6611 www.muiscientific.com mail@muiscientific.com

- 4 Segments
- Each Segment
  - 1 Aspiration Port
  - 3 Motility/manometry
- Record/Sample for 11 hrs.
- 7 hrs. post dose
  - Ibuprofen (RLD)

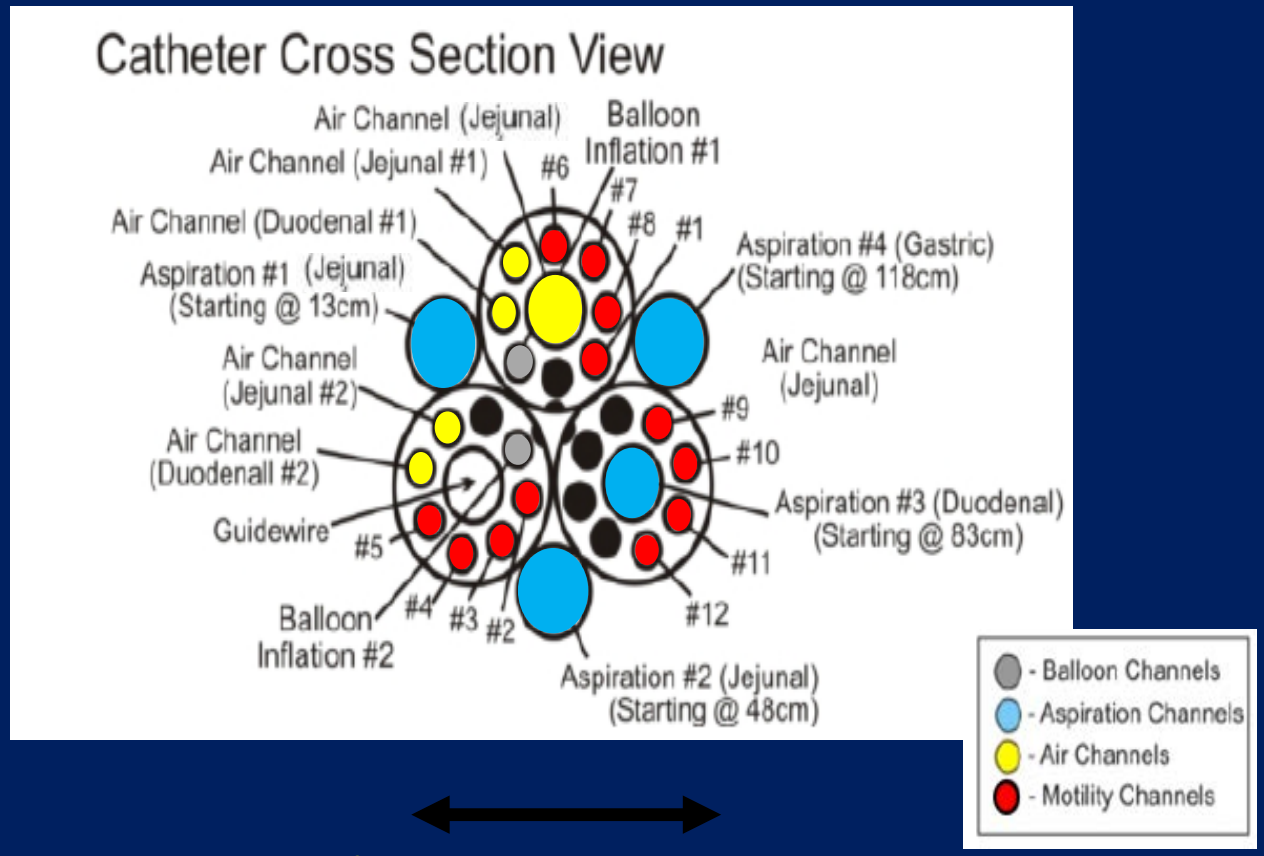
FDA ‘Orange Book’: Atenolol



New BE Science

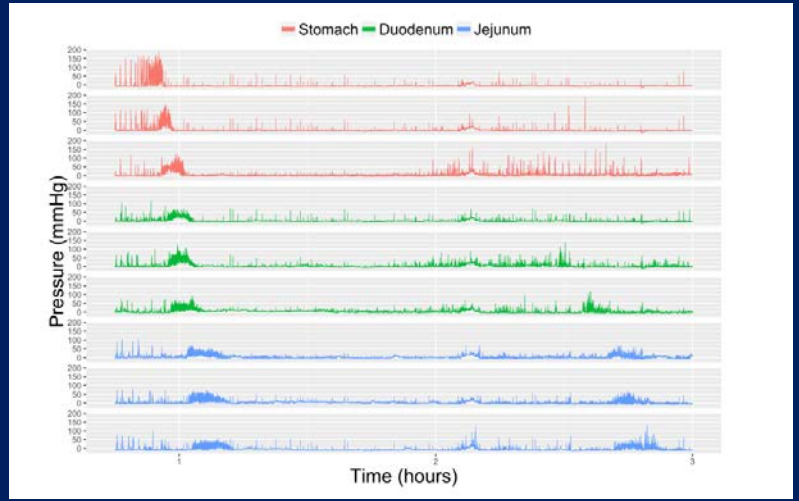
- Scope
- Plasma Levels
- GI Levels
- Motility
- What's 'New'
  - Intra and Inter subject Variability
  - GI Transit/Motility and plasma variability
  - pH individual Variability and Buffer
  - Gastric Model

Gastrointestinal Motility



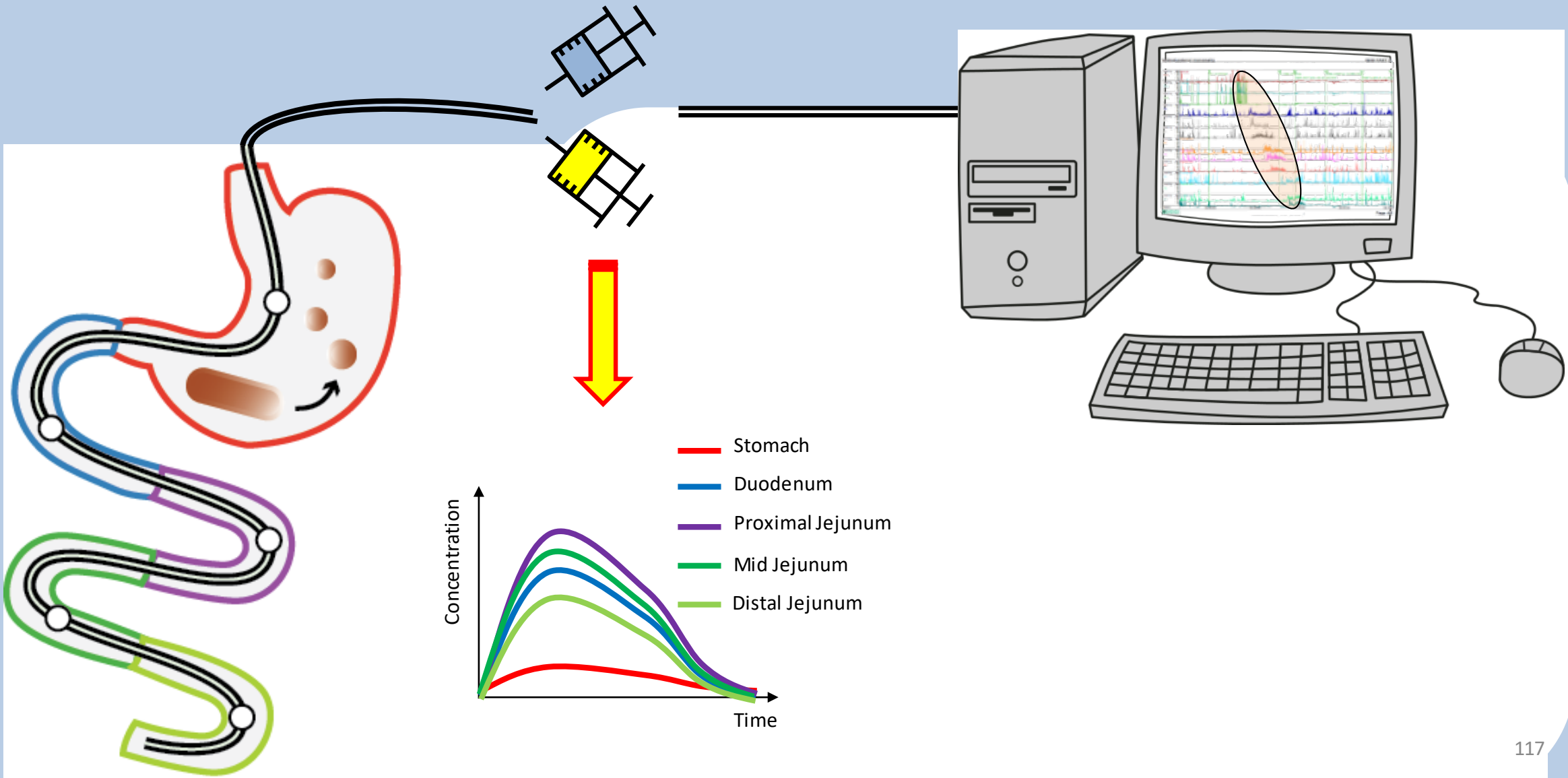
Diameter ~ 7mm

GI Motility Recording (Fasted)



1) Gastrointestinal Concentrations

2) Motility Contractions

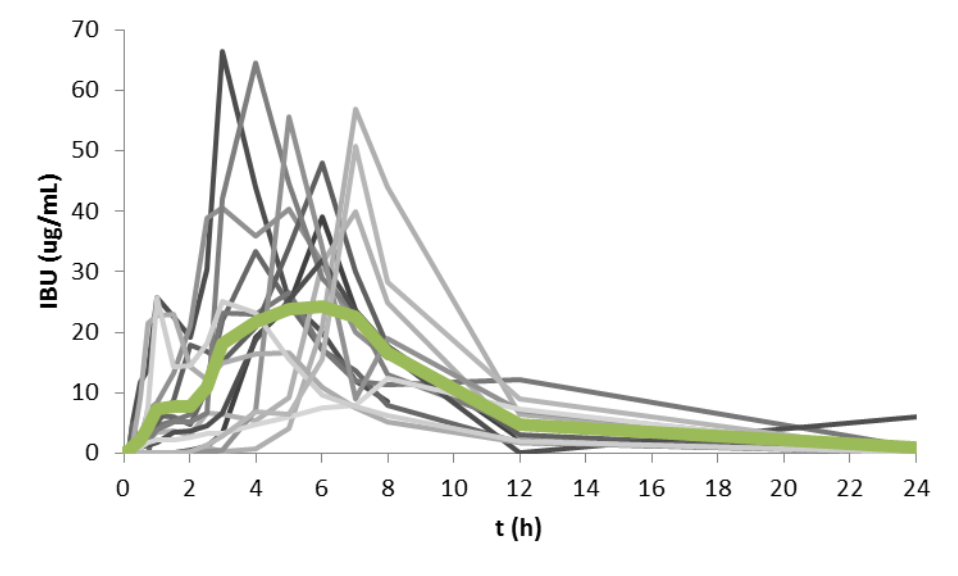


Fed State: Administration of Liquid Meal

- Volume of Pulmocare®/calories administered by each volunteer:

Subject ID	Administered volume Pulmocare (mL)	Administered Calories (Cal)
B002-P1	400	600
B002-P2	236.6	354.9
B008-P1	253.2	379.8
B020-P1	280	420
B020-P2	324	486
B022-P1	396	594
B022-P2	474	711
B026-P1	454	681
B031-P1	174	261
B034-P1	439	658.5
B041-P1	7	10.5
B043-P1	474	711
B043-P2	474	711
B046-P1	374	561
B060-P1	469	703.5
B060-P2	474	711
B066-P1	359.2	538.8
Averages	**372,3571429**	**586,0909091**
Range:	**7 - 474**	**10.5 - 711**

Plasma Ibuprofen (Fed: n = 15)



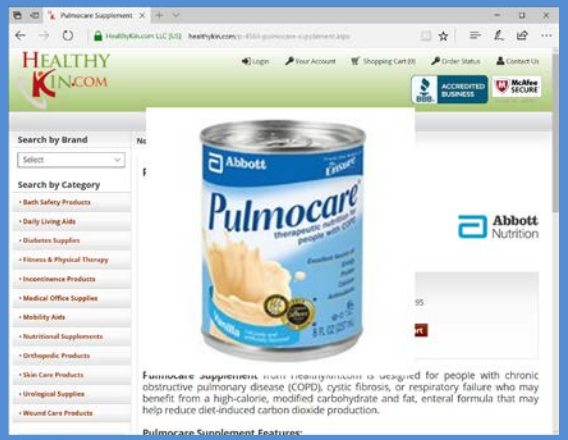
This Study

	Cmax		Tmax		AUC0-t	
	FASTED	FED	FASTED	FED	FASTED	FED
GeoMean	54	38	-	-	257	198
Mean	57	41	-	-	274	208
SD	18	16	-	-	95	65
CV	32	39	-	-	35	31
Median	-	-	3	5	-	-
Range	-	-	1 - 8	1 - 8	-	-
Fed/Fasted	0.69		1.67		0.77	

Literature

	Cmax*		Tmax		AUC*	
	fasted	fed	fasted	fed	fasted	fed
Geisslinger 1989	68	60	0.89	1.55	275	225
Kapil 2004	68	58	1.80	2.10	246	234
Klueglich 2005	68	52	1.40	1.60	234	184
Tanner 2010	64	49	1.25	2.00	218	236
Levine 1992	84	64	1.30	1.60	268	233
Mean	70	57	1.33	1.77	248	223
Fed/Fasted	0.81		1.33		0.90	
* - values adjusted to 800 mg						

Liquid Meal (~350 Cal)



anatomy & in vitro model