Advances in BA/BE and Dissolution Methodology

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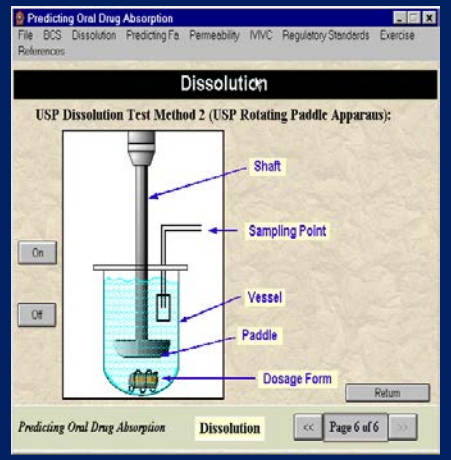
2010

1950

1970



GDUFA: 5-24-18

Product Research Advances

- GastroIntestinal Processes
  - pH, Buffer Capacity, Motility
  - Enteric Coating
- Gastrointestinal Simulator (GIS)
  - In vivo Predictive Dissolution (iPD)
- In Vivo Plasma Level Variability

GastroIntestinal Prediction

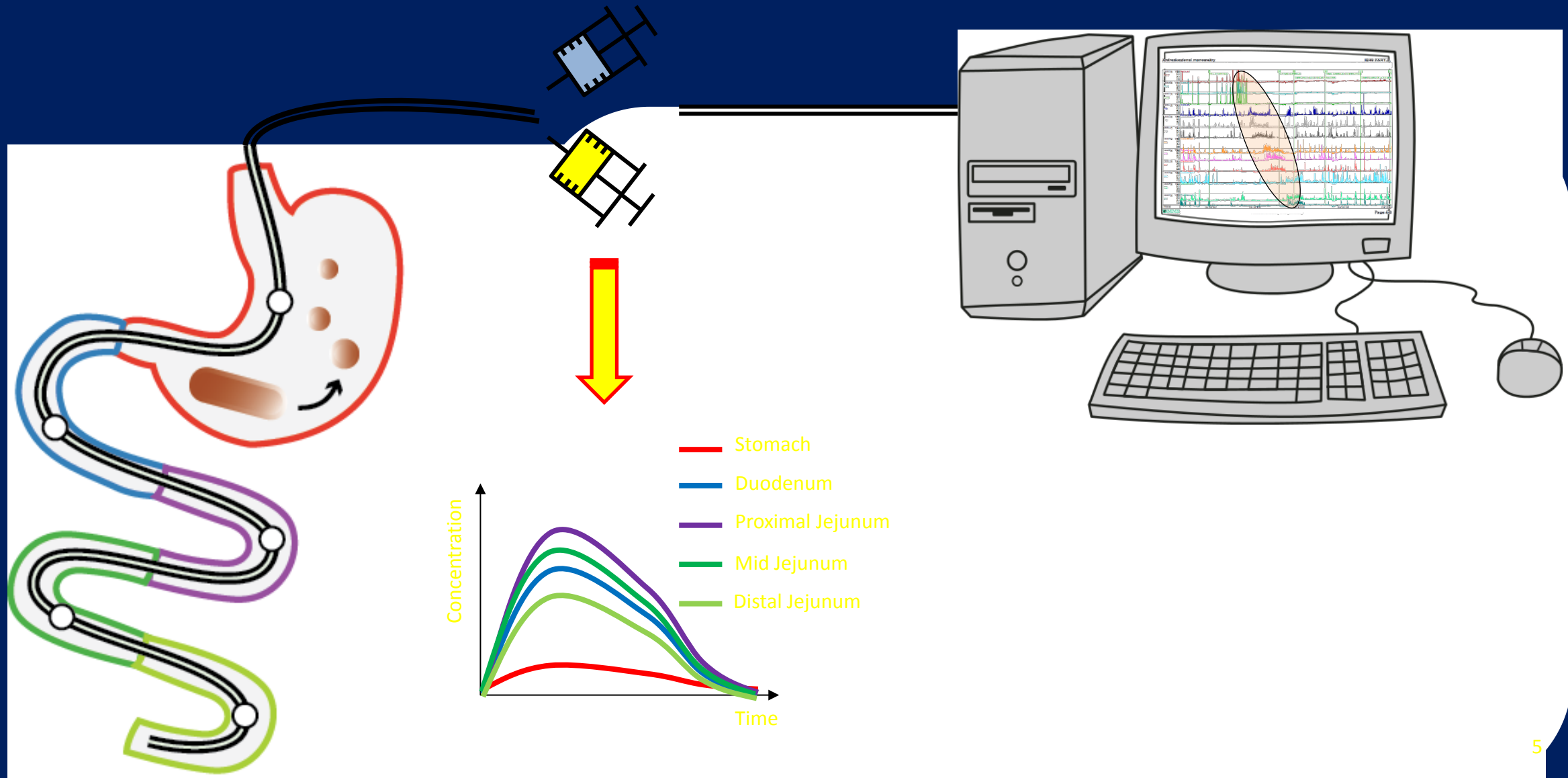
Required Accurate Input

Ongoing Studies

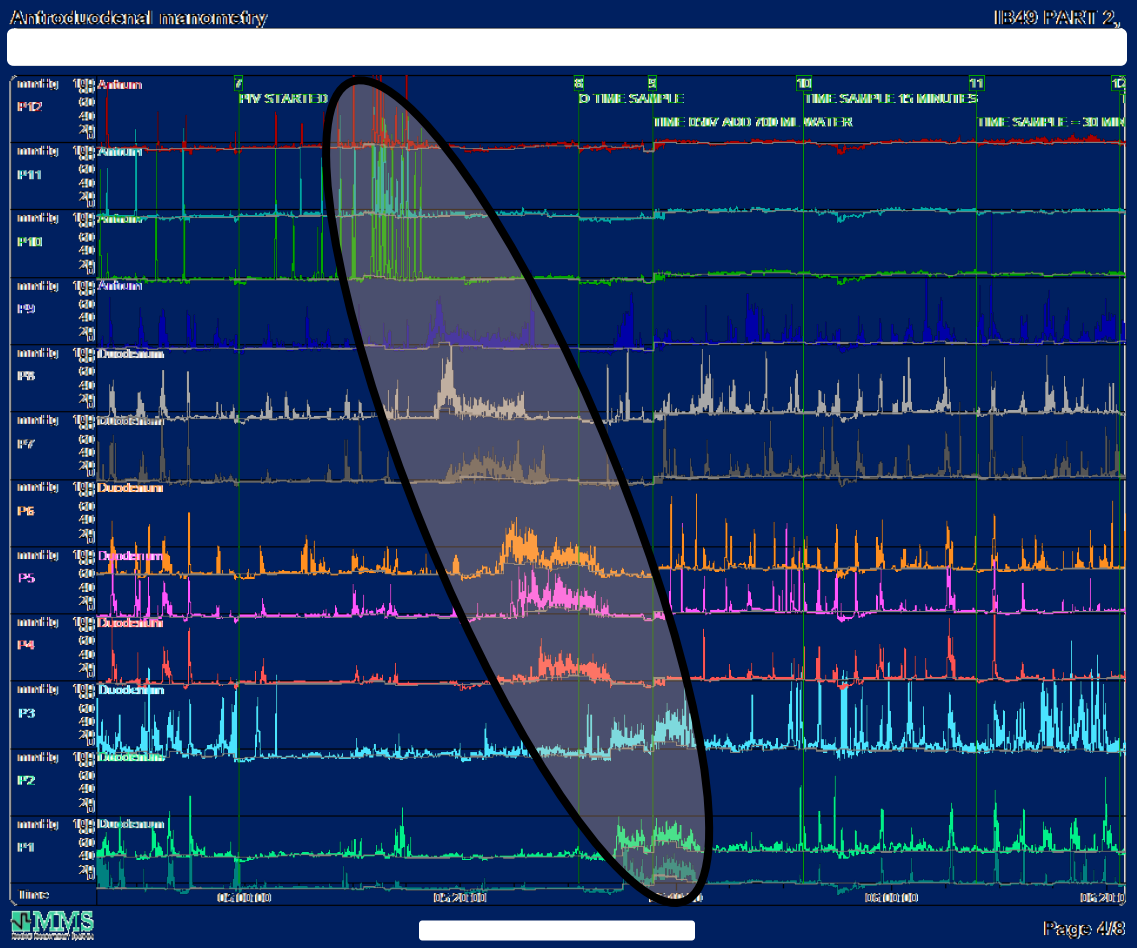
DIRECT AND SIMULTANEOUS DRUG MEASUREMENT: PLASMA AND INTESTINE (NORMAL SUBJECTS, BE PROTOCOL)

1) Gastrointestinal Concentrations

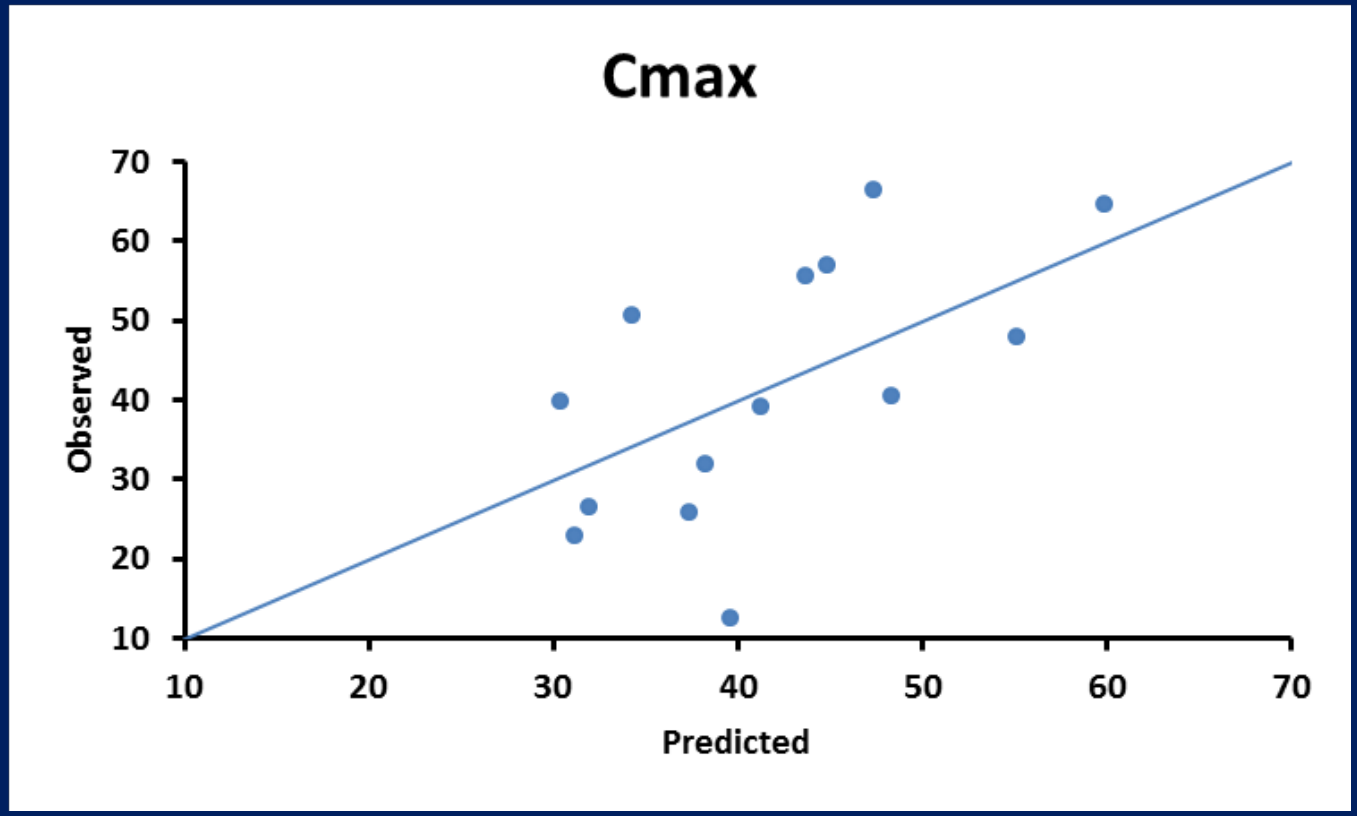
2) Motility Contractions



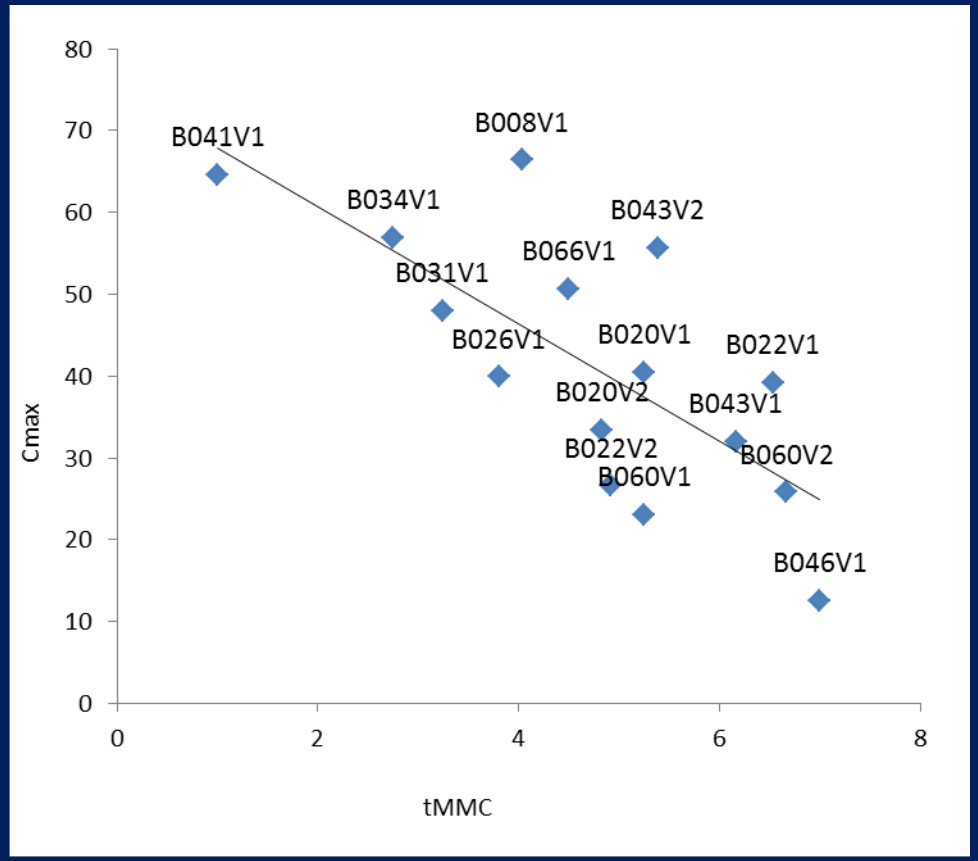
Gastrointestinal Motility: Fasted

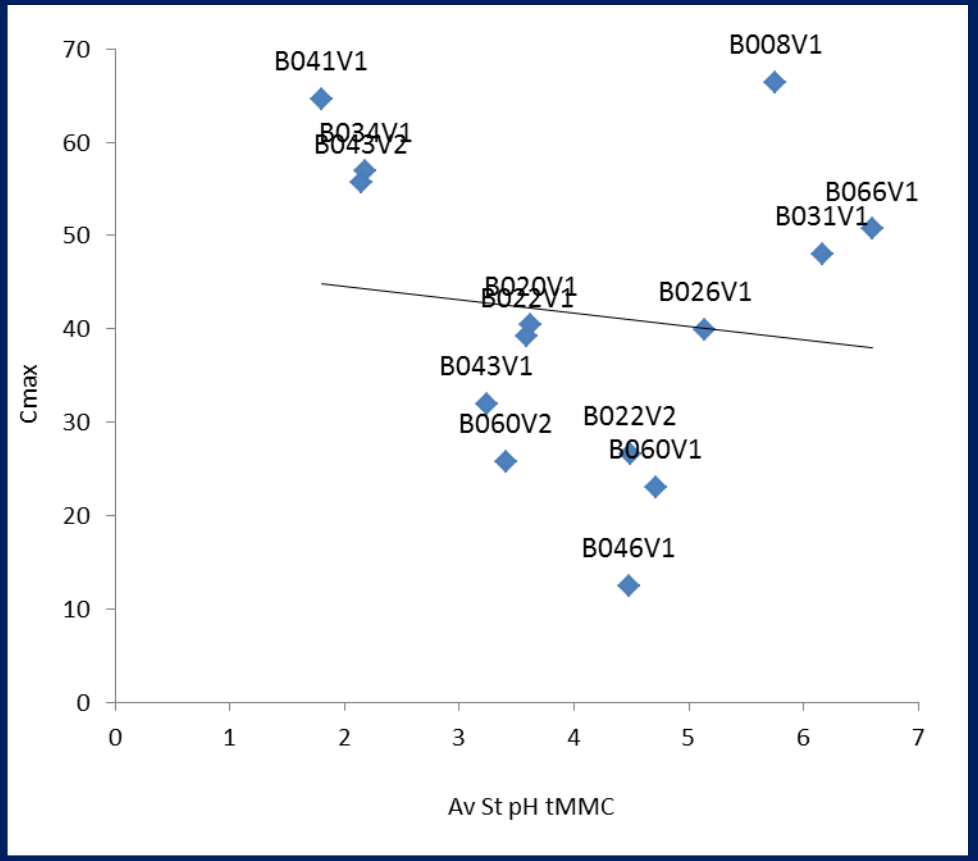


Combined Models Prediction

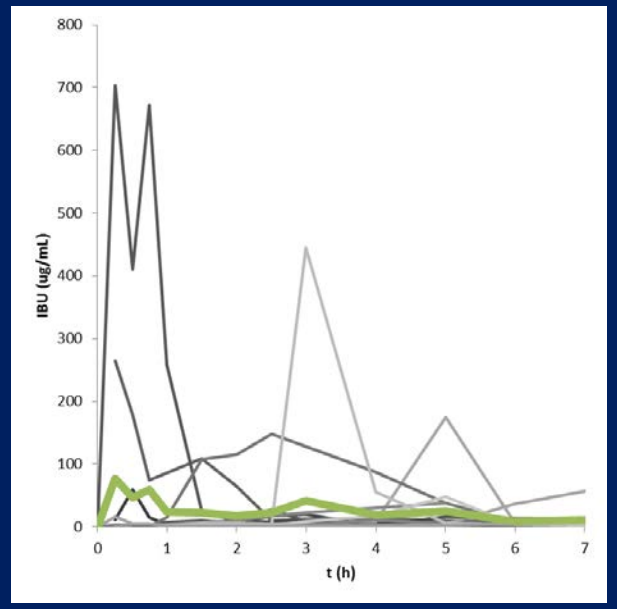


Initial Correlations

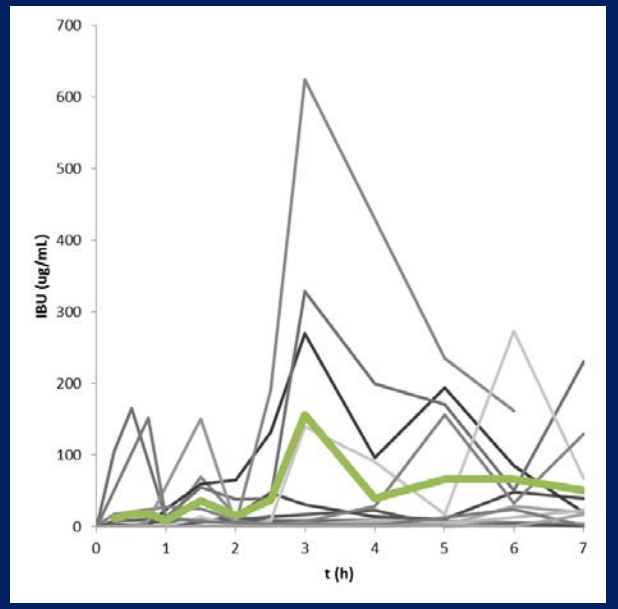




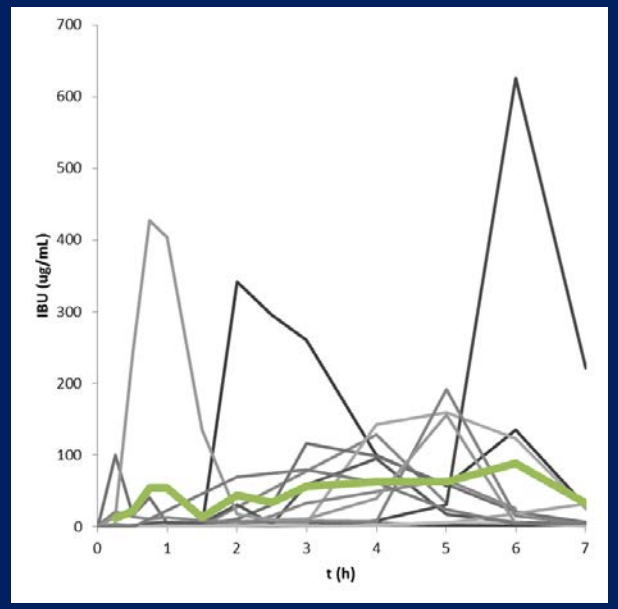
Luminal GI Ibuprofen (solution)



Stomach



Duodenum



Jejunum

Ibuprofen Present in the Intestine for 7 hrs.

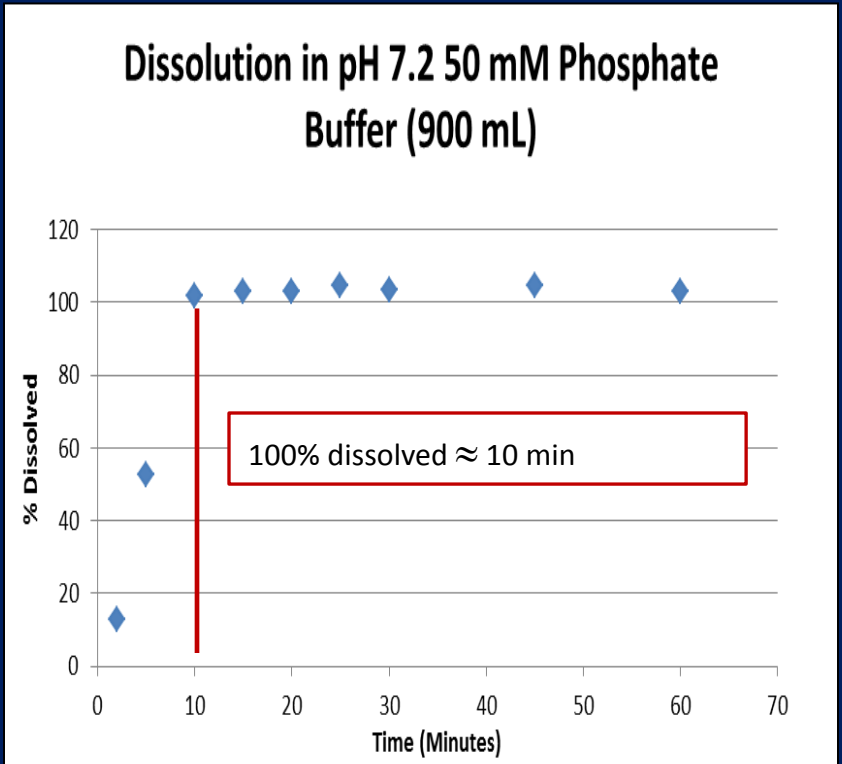
First Observation

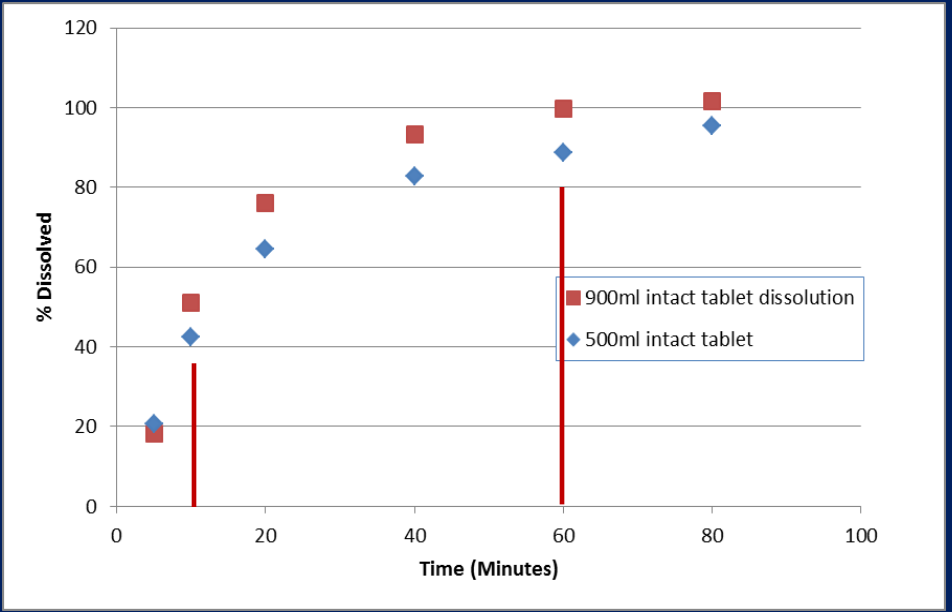
Ibuprofen is in the intestine for 7 hours
Yet Dissolves in 10 minutes (USP)

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

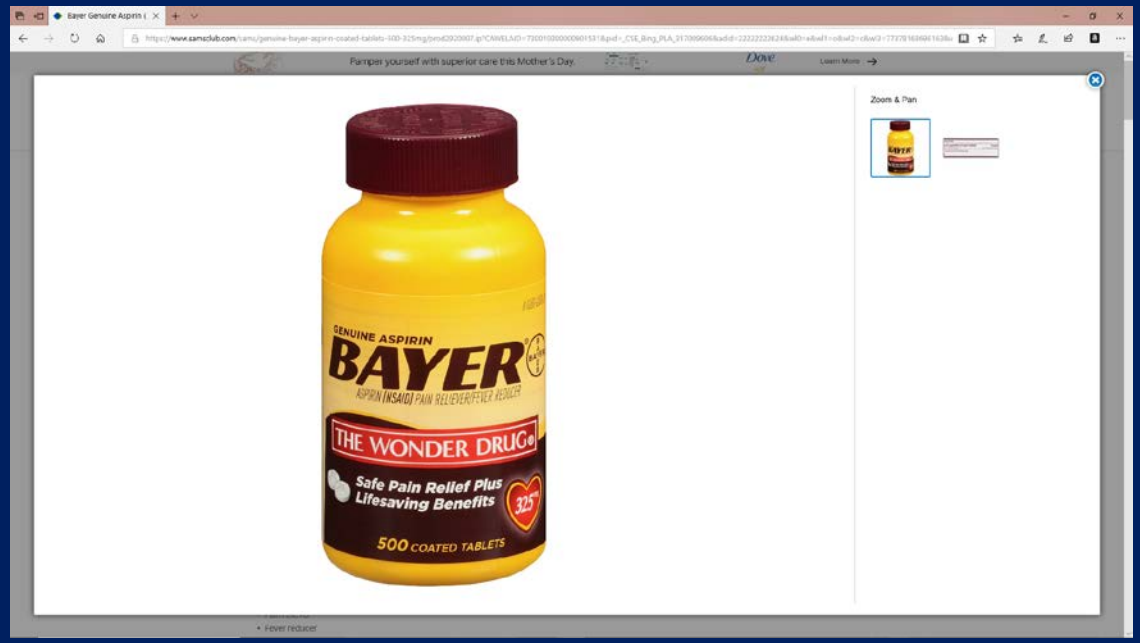
USP Test: pH =7.2 50mM Phoshate
50 RPM paddle (Apparatus 2)
Not Less Than 80% dissolved in 60 min

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

Low Dose ASPIRIN



DOI: 10.1161/CIRCULATIONAHA.112.117283

Drug Resistance and Pseudoresistance:

An Unintended Consequence of Enteric Coating Aspirin

Running title: *Grosser et al.; Aspirin Resistance and Pseudoresistance*

Tilo Grosser, MD*[1]; Susanne Fries, MD*[1]; John A. Lawson, MS[1]; Shiv C. Kapoor, PhD[1]; Gregory R. Grant, PhD[1,2,3]; Garret A. FitzGerald, MD[1]

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Journal Subject Codes: [118] Cardiovascular Pharmacology; [122] Secondary prevention; [71] Antiplatelets; [92] Platelets; [178] Aggregation

Asian population. Importantly, our findings support the use of lower BMI cutoffs to define obesity in Asian adults, by demonstrating the presence of LV structural and functional changes even at these lower cutoffs. Furthermore, lower BMI thresholds may be needed for public health action (e.g., encouraging weight loss and exercise) in Asian communities, and particularly among Asian women who have a lower BMI threshold for subclinical LV contractile dysfunction and steeper decline in LV mechanics with increasing BMI and WC. The implications of our findings for the development of future heart failure deserve further study, particularly heart failure with preserved ejection fraction, which is increasingly recognized to include an obesity-related phenotype (4).

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http://dx.doi.org/10.1016/j.jacc.2017.04.016

Please note: Dr. Lam was supported by a Clinical Scientist Award from the National Medical Research Council; has received research support from Boston Scientific, Bayer, Thermo Fisher, Medtronic, and Vifor Pharma; and has served as a consultant for Bayer, Novartis, Takeda, Merck, AstraZeneca, Janssen Research & Development, LLC, Menarini, Boehringer Ingelheim, and Abbott Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.

2. Hung CL, Gonçalves A, Lai YJ, et al. Light to moderate habitual alcohol consumption is associated with subclinical ventricular and left atrial mechanical dysfunction in an asymptomatic population: dose-response and propensity analysis. J Am Soc Echocardiogr 2016;29:1043–51.

3. Piro M, Della Bona R, Abbate A, Biasucci LM, Crea F. Sex-related differences in myocardial remodeling. J Am Coll Cardiol 2010;55:1057–65.

4. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation 2016;134:73–90.

Collapse of the Aspirin Empire

Is it Diabetic Gastroparesis or Cardioprotective Paresis?

I have read with great interest the paper recently published in the *Journal* by Bhatt et al. (1). The investigators reported that a high proportion of patients treated with enteric-coated (EC) aspirin failed to achieve complete inhibition of thromboxane B2 generation due to incomplete absorption. Reduced bioavailability may contribute to "aspirin resistance" in patients with diabetes (1).

Diabetic gastroparesis (DG) is a clinical syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach. DG has been generally attributed to autonomic neuropathy and poorly controlled hyperglycemia. The prevalence of gastroparesis is reported to be 20% to 40% of patients with type 2 diabetes mellitus (T2DM) (2). DG can result in many consequences such as impaired glucose regulation, hypoglycemia, decrease drug absorption, nutritional compromise, and a high rate of hospitalizations and poor quality of life (3). DG is associated with coronary artery disease, cardiovascular autonomic dysfunction, and microvascular complications such as peripheral neuropathy and retinopathy. Poor long-term glycemic control, such as elevated hemoglobin A_{1c} and body mass index, were independent predictors of DG (4). Recently, Saito et al. (5) reported that low-dose aspirin irrespective of EC did not affect the risk for cardiovascular events but increased the risk for gastrointestinal bleeding in patients with T2DM in a primary prevention setting.

Growing evidence has demonstrated that EC aspirin therapy fails in primary prevention in patients with T2DM. On account of DG prevalence and adverse effect on drug absorption, DG should be considered as a part of aspirin resistance in patients with T2DM.

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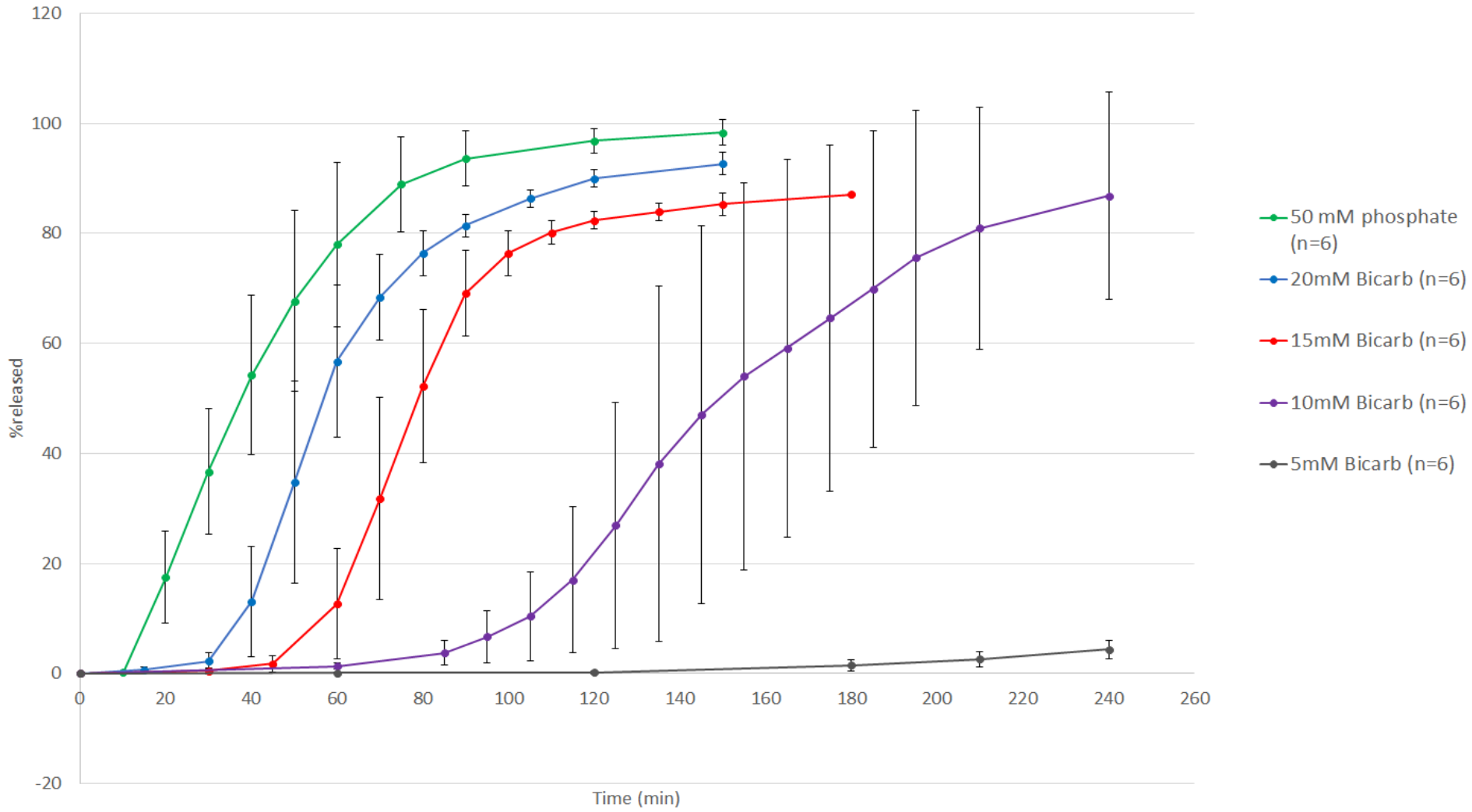
http://dx.doi.org/10.1016/j.jacc.2017.02.074

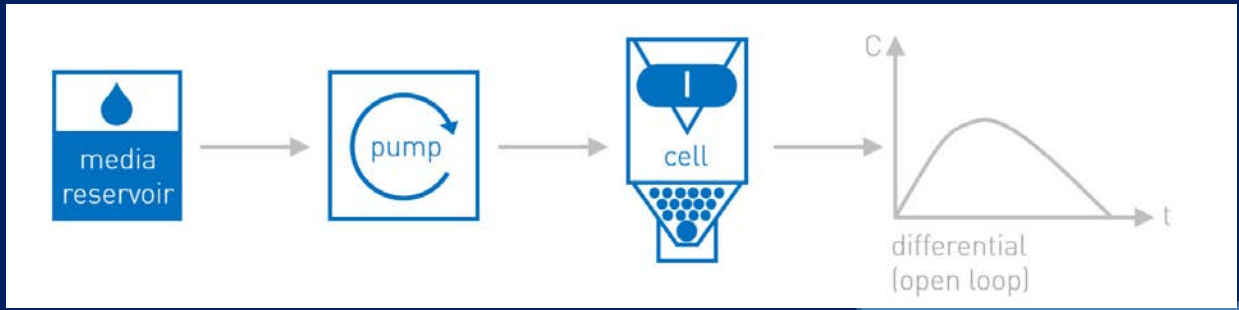
Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Figure 2. Dissolution Profiles of Bayer EC Aspirin 325 mg Tablets at pH 6.8 (mean±SD)



Small intestine as a flow through cell

In vitro flow cell



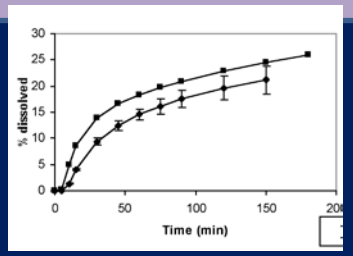
Differential profile

$\emptyset = fluid\ flow$

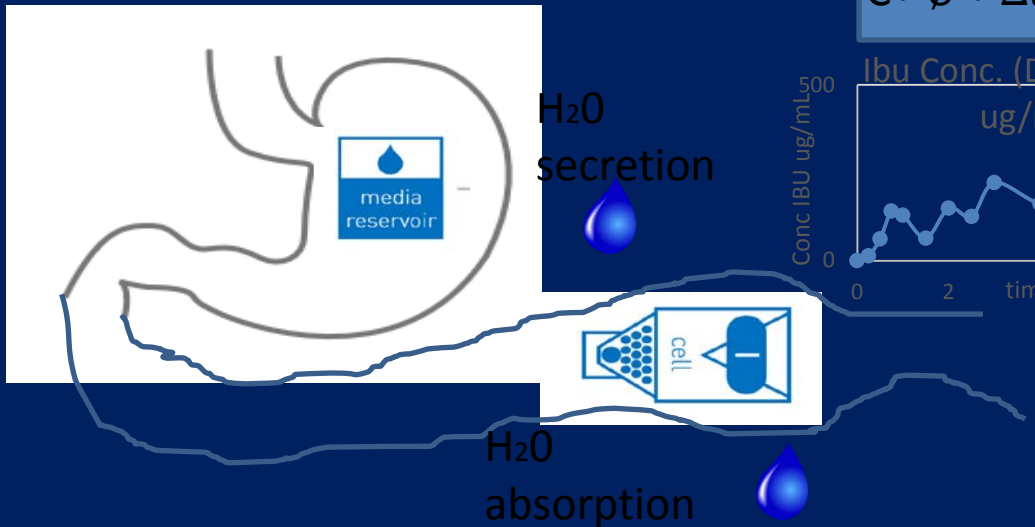
$C * \emptyset * \Delta t = Amount$

Cumulative profile

$Fdiss_t = \sum_0^t (Amount/Dose)$



In vivo flow cell



Differential profile

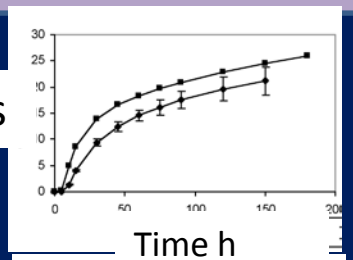
$\emptyset = fluid\ flow = "1"$

$C * \emptyset * \Delta t = Amount$

Cumulative profile

Individual $Fdiss_t = \sum_0^t (Amount/Amount_{max})$

Fdiss



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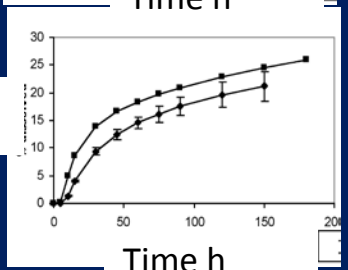

Koenigsknecht et.al., 2017

molecular pharmaceutics

Article

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In Vivo Dissolution and Systemic Absorption of Immediate Release Ibuprofen in Human Gastrointestinal Tract under Fed and Fasted Conditions

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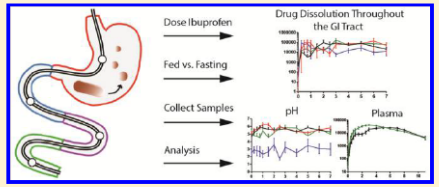
Supporting Information



ABSTRACT: *In vivo* drug dissolution in the gastrointestinal (GI) tract is largely unmeasured. The purpose of this clinical study was to evaluate the *in vivo* drug dissolution and systemic absorption of the BCS class IIa drug ibuprofen under fed and fasted conditions by direct sampling of stomach and small intestinal luminal content. Expanding current knowledge of drug dissolution *in vivo* will help to establish physiologically relevant *in vitro* models predictive of drug dissolution. A multilumen GI catheter was orally inserted into the GI tract of healthy human subjects. Subjects received a single oral dose of ibuprofen (800 mg tablet) with 250 mL of water under fasting and fed conditions. The GI catheter facilitated collection of GI fluid from the stomach, duodenum, and jejunum. Ibuprofen concentration in GI fluid supernatant and plasma was determined by LC−MS/MS. A total of 23 subjects completed the study, with 11 subjects returning for an additional study visit (a total of 34 completed study visits). The subjects were primarily white (61%) and male (65%) with an average age of 30 years. The subjects had a median [min, max] weight of 79 [52, 123] kg and body mass index of 25.7 [19.4, 37.7] kg/m^2. Ibuprofen plasma levels were higher under fasted conditions and remained detectable for 28 h under both conditions. The AUC_{0-24} and C_{max} were lower in fed subjects vs fasted subjects, and T_{max} was delayed in fed subjects vs fasted subjects. Ibuprofen was detected immediately after ingestion in the stomach under fasting and fed conditions until 7 h after dosing. Higher levels of ibuprofen were detected in the small intestine soon after dosing in fasted subjects compared to fed. In contrast to plasma drug concentration, overall gastric concentrations remained higher under fed conditions due to increased gastric pH vs fasting condition. The gastric pH increased to near neutrality after feeding
continued...

Special Issue: Industry-Academic Collaboration in Oral Biopharmaceutics: The European IMI OrBiTo Project

Received: May 22, 2017
Revised: September 5, 2017
Accepted: September 22, 2017
Published: September 22, 2017

DOI: 10.1021/acs.molpharmaceut.7b00425
Mol. Pharmaceutics 2017, 14, 4295−4304

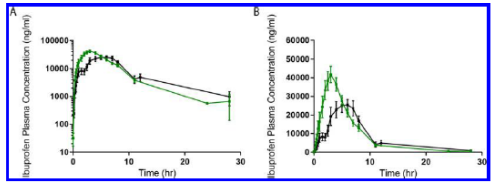


Figure 1. Average plasma concentration vs time profiles of ibuprofen. Fasted (n = 20, green line) and fed (n = 14, black line) conditions plotted in (A) logarithmic and (B) linear scale. Error bars indicate the standard error of the mean (SEM). Data from fasted subjects (n = 20) and fed subjects (n = 14) are shown.

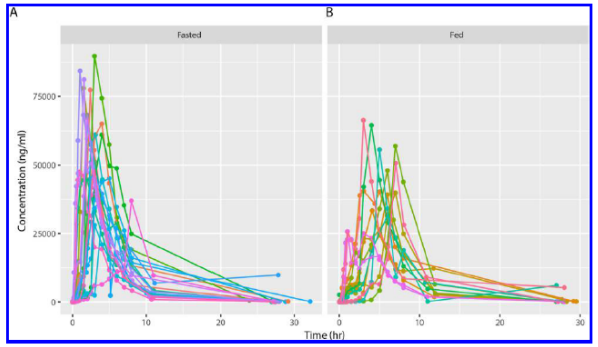


Figure 2. Individual plasma concentration vs time profiles of ibuprofen under (A) fasted and (B) fed conditions. Each line represents an individual subject.

Table 2. Plasma Pharmacokinetic Parameters of Ibuprofen (Mean ± Standard Deviation), Including Area under the Curve from Time Zero to 24 h (AUC_{0-24}), Maximum Concentration (C_{max}), and Time to C_{max} (T_{max})[a]

study arm	no. of observations	AUC_{0-24} (μg·h/mL)	C_{max} (μg/mL)	T_{max} (h)
fasted	20	241.888 ± 88.907	58.247 ± 18.400	2.980 ± 1.613
fed	14	229.452 ± 76.879	43.051 ± 14.312	4.694 ± 1.994
statistical significance		p = 0.020	p = 0.025	p = 0.010

[a]Significance was determined using the nonparametric Kruskal−Wallis equality-of-populations rank test.

a semilogarithm plot and as absolute values by fasted and fed states. Individual concentration−time profiles of subjects by fasted and fed conditions are shown in Figure 2. In both the fasted and fed conditions ibuprofen was detected in the plasma 10 min after administration of ibuprofen. As shown in Figures 1 and 2, the C_{max} was lower and T_{max} longer in the fed versus fasted state.

Fed subjects had a significantly (p = 0.020) lower AUC_{0-24} value than those in the fasted condition, though this difference was a mean of 5.42% lower. In contrast, the difference in C_{max} was 35.2% lower (p = 0.025) in the fed versus fasted conditions. This lower C_{max} was also associated with a longer T_{max} that was a mean of 1.71 h longer in the fed condition. The specific values and statistical comparison of these parameters are provided in Table 2. To quantify intrasubject variability, we analyzed the AUC_{0-24} from the 11 subjects that completed two separate study visits under the same treatment conditions. The geometric mean

DOI: 10.1021/acs.molpharmaceut.7b00425
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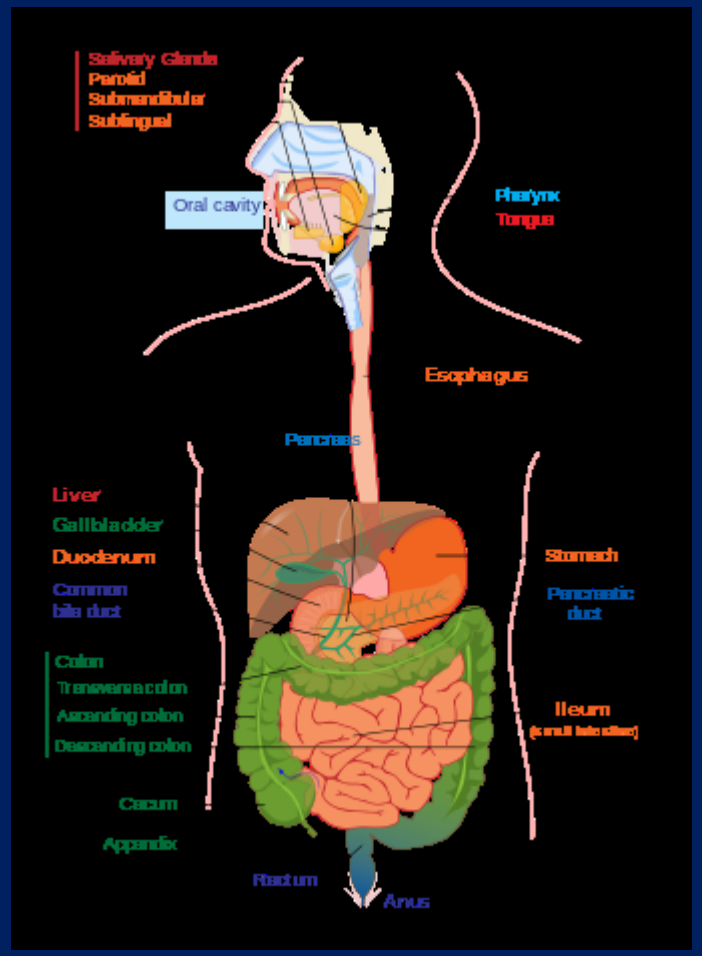
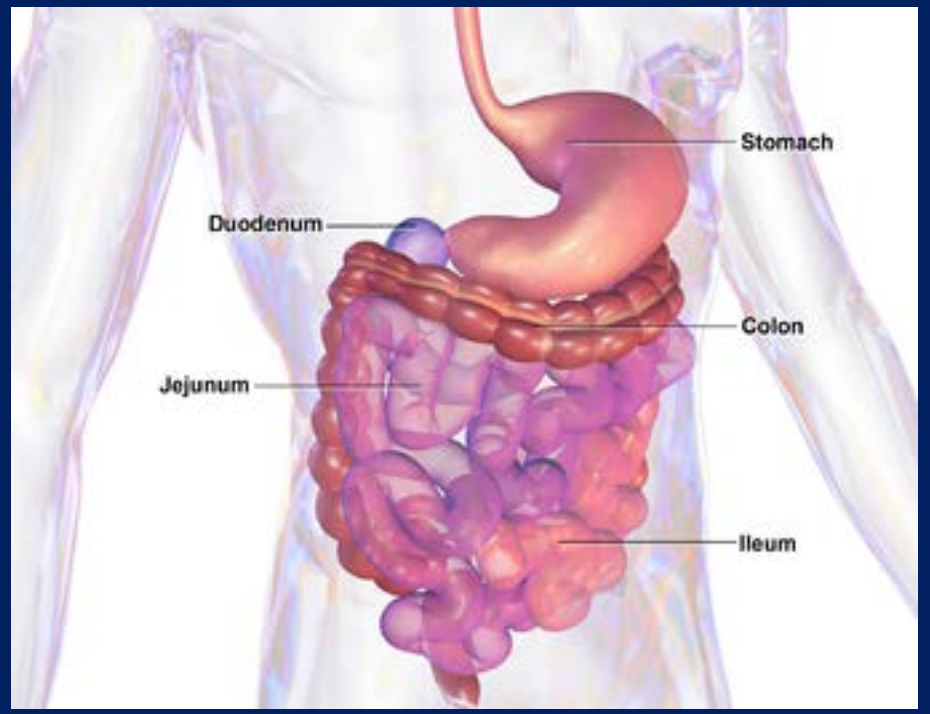
Human Gastrointestinal Tract

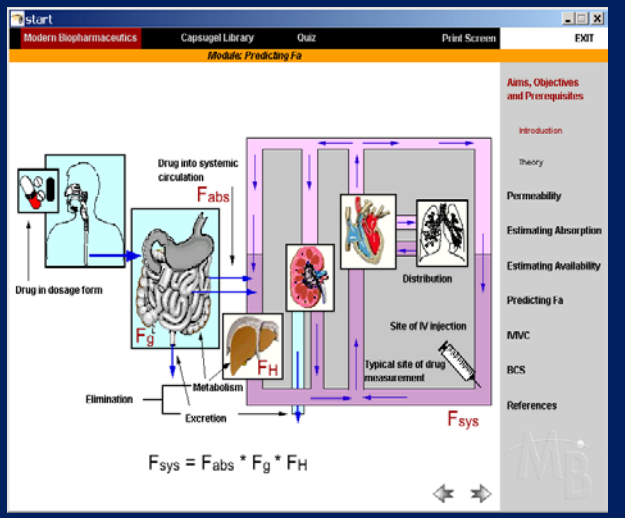




Product Research (FDA)

- Measure Gastrointestinal Mechanism
  - Buffer Capacity
  - Buffer is Bicarbonate
- Motility State is a Random Variable
  - Requires a Stochastic Process
  - MRI Development
- Ultimately Reduce BE Variability
- Capture in a GIS Dissolution Methodology

BCS: In Vivo->in Vitro



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