Advancing the Science of Oral Solid Dosage Form Development and Performance

and away from "Guided Empiricism"

November 7, 2018

Gregory E. Amidon, Ph.D.

Session Description and Objectives

This talk will cover several aspects of scientific oral solid dosage form design based on an understanding of the critical physical, chemical, and mechanical properties of pharmaceutical ingredients. In addition, recent advances in our understanding of in vivo conditions is providing greater appreciation of in vivo environment in which dosage forms must perform. This allows us to imagine more in vivo relevant dissolution test methods.

- Relate physical, chemical, and mechanical properties to oral product design and development.
- Understand oral in vivo environment and its impact on drug dissolution.
- Envision more in vivo predictive dissolution methods.

Biography and Contact Information

- 11 years as Research Professor of Pharmaceutical Sciences
  College of Pharmacy, University of Michigan, Ann Arbor, MI 48109
- 28 years of industrial experience (Upjohn, P&U, Pharmacia, Pfizer)

- Contact Information: geamidon@med.umich.edu

  2062 College of Pharmacy

  428 Church Street

  University of Michigan

  Ann Arbor, MI 48109-1065

Acknowledgements

- Deanna Mudie, PhD — Lonza (Bend Research)
- Brian J. Krieg, PhD — Perrigo Pharmaceuticals
- Arjang Talattof, PhD — Scape Technologies Ltd
- Hao Xu, PhD — Postdoctoral Fellow, Abbvie
- Jozef Al-Gousous — Postdoctoral Fellow, U-M
- Bart Hens — Postdoctoral Fellow, U-M
- Patrick D. Sinko — Graduate Student
- Nicholas Job — Graduate Student
- Niloufar Salehi — Graduate Student
- Pirinka Georgiev — Undergraduate BSPS student
- Meagan Dean — Undergraduate BSPS student
- Sarah Harris — Undergraduate BSPS student
- Yue Yuan — Undergraduate BSPS student
- Troy Halseth — Undergraduate BSPS student
- Ava Dalton — High school student
- Hiro Tsume, PhD — Research Scientist, U-M
- Kazuki Matsui, PhD — Visiting Scientist
- Susumu Takeuchi, PhD — Visiting Scientist
- Naoto Igawa — Visiting Scientist
- Gordon Amidon, PhD — Professor, U-M
- Randy J. Wald RPh — GIS Interface, consultant

Financial Support Provided by:

- Chingju Wang Sheu — Graduate Student Fellowship
- Everett N. Hiestand — Graduate Student Fellowship
- Abbott — 2008-2011
- Abbvie — 2015-2019
- USP Fellowship — 2010-2012
- AstraZeneca — 2012-2013
- FDA Contract HHSF223201310144C: 2013-2016
- FDA Contract HHSF223201510157C: 2016-2018

NIH R01 GM107146 2014-2018

Science can do better than I don't know for an answer.

Some questions I've tried to answer

Drug/Maerial properties

- What particle size (and size distribution) do I need to achieve satisfactory content uniformity for a tablet formulation?
- What particle size do I need to achieve adequate dissolution in vitro and in vivo?

Mechanical properties

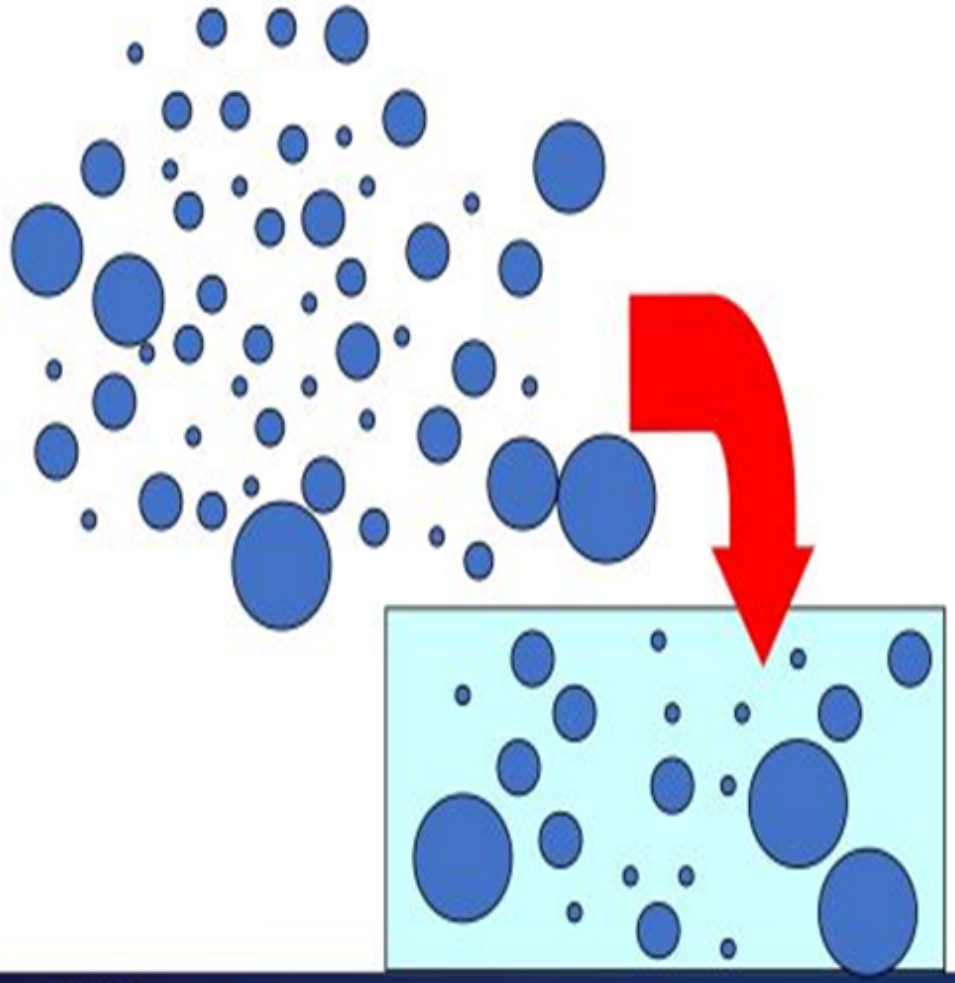
- How can we characterize and use the mechanical properties of a pharmaceutical material?
- How much of a non-brittle excipient do I need to add to a formulation containing a very brittle drug?
- What are critical material attributes of excipients (Excipient Performance)?
- How can we more efficiently develop a tablet dosage form quickly, confidently, and with a small amount of drug?

Product properties

- What are the critical processing parameters that impact formulation CQA?
- How will an oral dosage form perform in vivo?

For example, physical properties: What particle size do I need to achieve satisfactory content uniformity?

API with known particle size distribution



Particles end up in a tablet based on "random chance"

Simplifying Assumptions

- Log normal distribution
- Drug load is low
- No segregation

Theory

References

- Johnson MRC 1972. Particle size distribution of the active ingredient for solid dosage forms of low dosage. Pharm Acta Helv 47:546.
- Yalkowsky SH, Bolton S 1990. Particle Size and Content Uniformity. Pharm Res 7(9):962.

$$d'_g = \sqrt[3]{\left(\frac{6 \cdot D}{\pi \cdot \rho}\right) \cdot e^{-4.5 \cdot \ln^2 \sigma_g} \cdot \left(\frac{C_v}{100}\right)^2 \cdot 10^3}$$

d'_g = geometric mean diameter

D = dose, mg

σ_g = geometric standard deviation

ρ = true density

C_v = Coefficient of variation to pass CU criteria (C_v =3.84 to pass USP CU with 99% confidence)

Rohrs BR, Amidon GE, Meury RH, Secreast PJ, Skoug CJ, et al. 2006. Particle size limits to meet USP content uniformity criteria for tablets and capsules. Journal of Pharmaceutical Sciences 95(5):1049-1059.

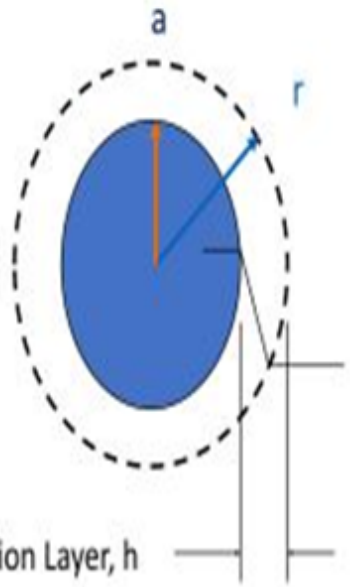
What particle size do I need to achieve adequate dissolution in vivo?

Very simple dissolution mass transport equation for spherical particles
Higuchi Hiestand Equation

$$\frac{dM}{dt} = 4\pi Da\Delta C$$

Major Assumptions:

- log normal distribution (d_g, σ_g)
- Sink conditions
- Diffusion layer thickness $\approx \infty$
- Other assumptions for impact of hydrodynamics are possible
  - Diffusion layer thickness:
    - h = particle radius
    - h_{max} = 30 um



Reference:

- W.I. Higuchi and E.N. Hiestand. Dissolution rates of finely divided drug powders I. Effect of a distribution of particle sizes in a diffusion-controlled process. J Pharm Sci. 52:67-71 (1963).
- R.J. Hintz and K.C. Johnson. the effect of particle size distribution on dissolution rate and oral absorption. Int J Pharm. 51:9-17 (1989).

% dissolved in 30 min in USP Apparatus 2
Rapidly disintegrating Tab. (Solubility, d_g, σ_g)

Saturated Solubility	Geometric Mean Diameter	Percent Dissolved at 30 Minutes			
		σ_g = 1.5	σ_g = 2.0	σ_g = 2.5	σ_g = 3.0
1 µg/mL	5 µm	76	70	67	65
	25 µm	6.1	10	14	18
	75 µm	0.7	1.3	2.4	3.8
5 µg/mL	5 µm	99	94	89	86
	25 µm	27	34	37	39
	75 µm	3.6	6.2	8.5	13
10 µg/mL	5 µm	100	98	94	91
	25 µm	46	49	50	50
	75 µm	7.2	11	16	19
50 µg/mL	5 µm	100	100	99	98
	25 µm	91	83	78	76
	75 µm	32	38	41	42
100 µg/mL	5 µm	100	100	100	99
	25 µm	98	93	88	84
	75 µm	53	55	55	55
500 µg/mL	5 µm	100	100	100	100
	25 µm	100	100	98	97
	75 µm	98	91	87	84
1000 µg/mL	5 µm	100	100	100	100
	25 µm	100	100	100	99
	75 µm	100	98	95	92

Amidon GE. 2011. Oral Solid Dosage Forms. In Sinko P, editor Martin's Physical Pharmacy and Pharmaceutical Sciences, 6th ed.: Wolters Kluwer. p 563-593.

How can we characterize and use the mechanical properties of a pharmaceutical material?

Solid dose formulation ingredient and process selection requires an understanding of:

- Mechanical properties of API and excipients
- Properties of mixtures
- Impact of processing

Mechanical Properties = properties of a material under an applied stress or after a stress has been applied.

Mechanical Properties

- Elasticity (stiffness)
- Plasticity (hardness)
- Viscoelasticity
- Brittleness
- Strength (tensile)
- Bonding

Mechanical Property Characterization methods

Quasi-static testing

- Prepare test specimen
  - Slow compression, decompress
- Test after compression
  - Apply "Engineering" type tests (eg: brittleness, hardness, elasticity)

Dynamic testing

- Test during compression
  - Often "high" speed"
- Utilize:
  - Compaction Simulator
  - Instrumented Tablet Press

Measured Properties (Complimentary methods)

Quasi Static Measurements

Compression Pressure (CP)
Elasticity (E')
Dynamic Indentation Hardness (H_d)
Quasi-static Hardness (H_q)
Tensile Strength (TS)
Compromised Tensile Strength (TSo
Brittle Fracture Index (= fn(TS, TSo)
Bonding Index (=TS/Hd)
Strain Index (=Hd/E')
Degree of Viscoelasticity (= Hd/Hq)
Compressibility Index (CP-SF)
Tabletability Index (TS-CP)
Compactibility Index (TS-SF)

Dynamic Testing Measurements

Property
Compression Pressure (CP)
Tensile Strength (TS)
Solid Fraction (porosity) (SF)
Tablet Hardness
Tabletability profile (CP-TS)
Compressibility profile (CP-SF)
Compactibility profile (TS-SF)
Ejection Force
Machine Speed Effect
Tablet Press Simulation

Quasistatic Mechanical Properties of API and Excipients

Elastic Modulus

Material	Young's Modulus (GPa)	
Calcium carbonate	88	Stiff
Calcium phosphate	48	
Sorbitol	45	
Lactose Monohydrate	24	
Lactose Spray Process	14	
Theophylline	13	
Acetaminophen	12	
Microcryst. cellulose	10	
Caffeine	9	
Aspirin	8	
Pregelatinized Starch	6	
Ibuprofen	5	
Stearic acid	4	
Maize starch	4	Elastic

Deformation Pressure

Material	Dynamic Hardness, MPa	
Sucrose	1046	Hard
NaCl	653	
Lactose Monohydrate	515	
Acetaminophen	265	
Lactose beta anhydrous	251	
Ibuprofen Lot A	162	
Microcrystalline cellulose	168	
Aspirin	55	
Ibuprofen Lot B	35	
Magnesium Stearate	22	
Na Lauryl Sulfate	10	Soft

Brittle Fracture

Non-brittle

Material	BFI
Microcrystalline cellulose	0.03
Acetaminophen	0.03
Ibuprofen (lot A)	0.06
Lactose, Spray Dried	0.12
Aspirin	0.19
Caffeine	0.47
Phenacetin	0.43
Ibuprofen (lot B)	0.4
Starch	0.7
Erythromycin	0.7
Methenamine	0.8
U-54669F	1.3

Brittle

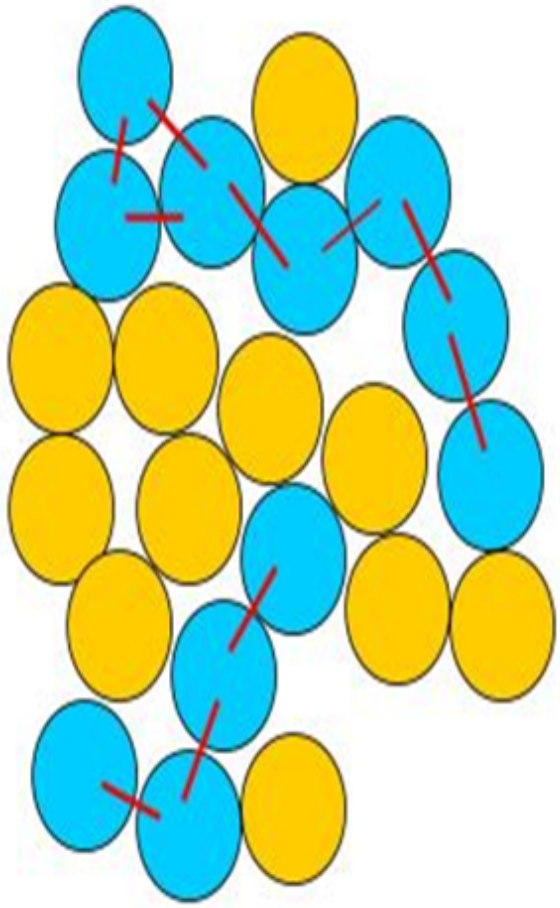
Properties of Formulations (Mixtures)

Binary Mixture Model (50-50 mix)

(equal sized monodispersed spheres)

Interaction		Theory	x = 0.5
A-A	10	x^2	0.25
B-B	9	$(1-x)^2$	0.25
A-B	16	$2x(1-x)$	0.5

X_i = volume fraction of i

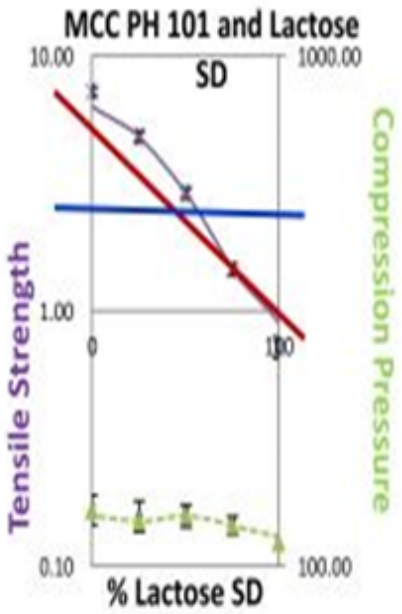


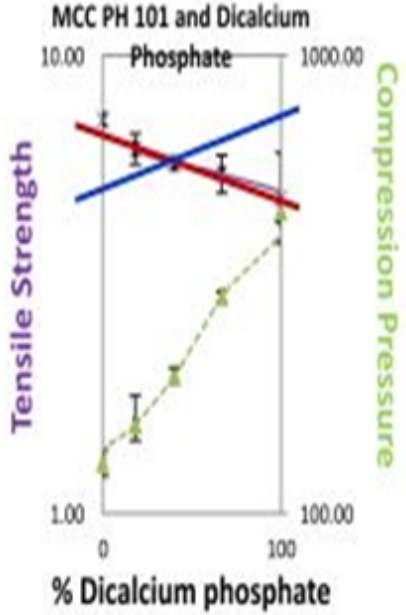
If $\Phi_{AB} = (\Phi_{AA} * \Phi_{BB})^{1/2}$ = Geometric Mean

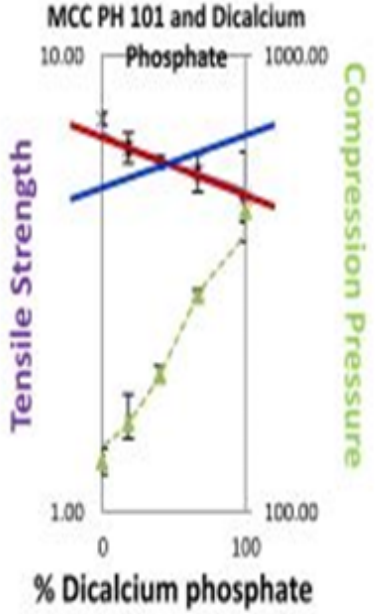
$$\log(\Phi_{mix}) \approx x_A \log(\Phi AA) + x_B \log(\Phi BB) = \Sigma x_i \log(\Phi_i)$$

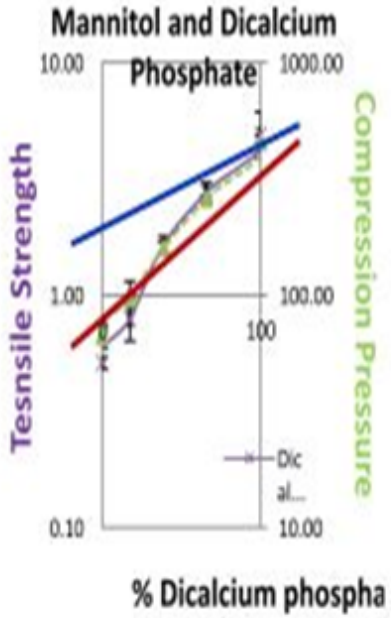
Example Binary Excipient Mixtures (Follow Power Law of Mixes)

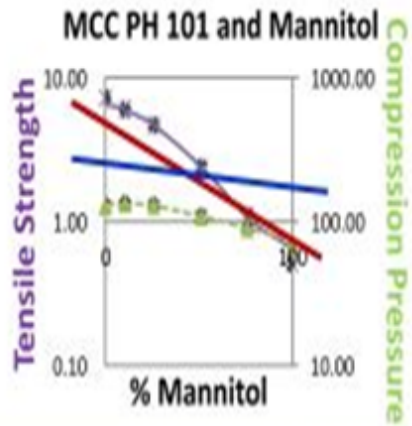
MCC, SDLactose, DiCal, Mannitol, Corn Starch

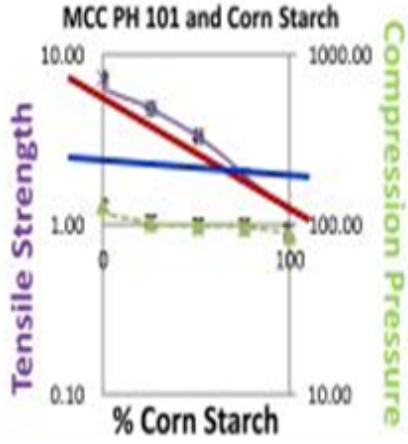


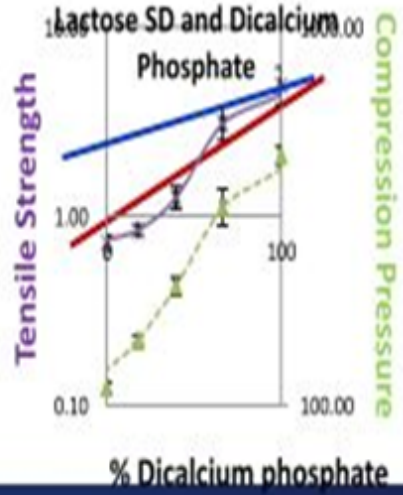








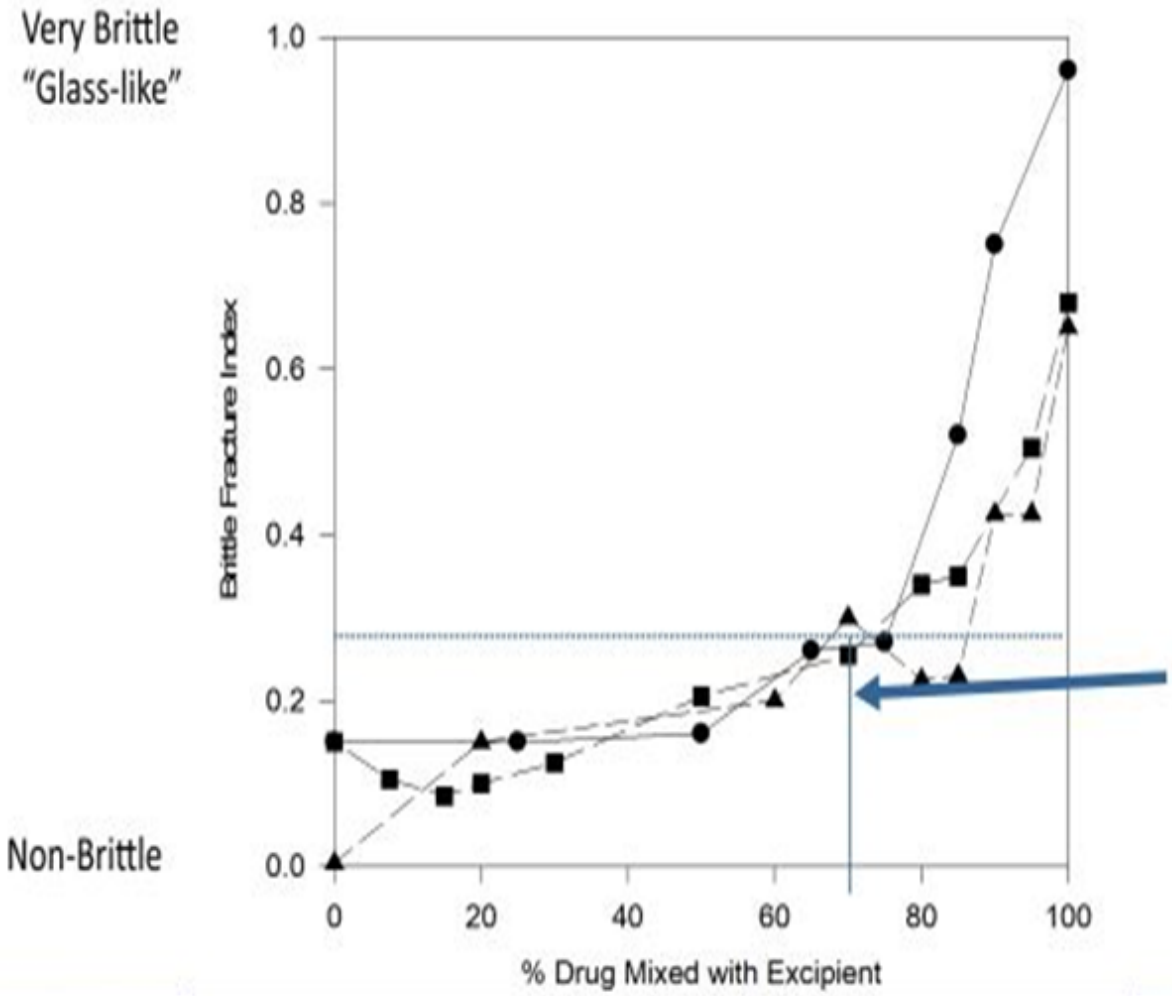




Amidon GE. 2011. Oral Solid Dosage Forms. In Sinko P, editor Martin's Physical Pharmacy and Pharmaceutical Sciences, 6th ed.: Wolters Kluwer. p 563-593.

Effect of the Addition of a Non-brittle Material to a Brittle Drug

(Methenamine, Flurbiprofen, Drug X



Adding only 30% of a non-brittle excipient makes the mixture much less brittle.

Formulation Mechanical Properties

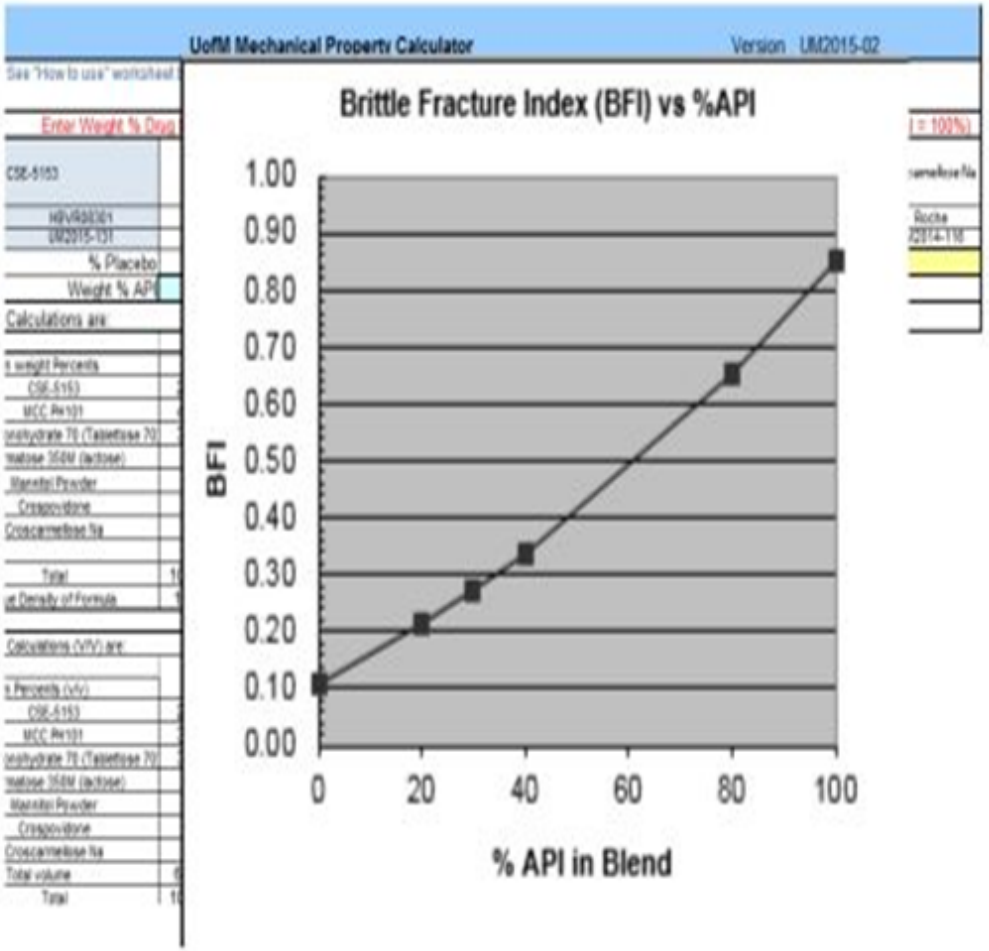
Formulation = Drug + Excipients

Reduce a multicomponent mixture to a binary mixture of:

Component 1: Drug

Component 2: Excipients

(eg: MCC + SDLactose +...)



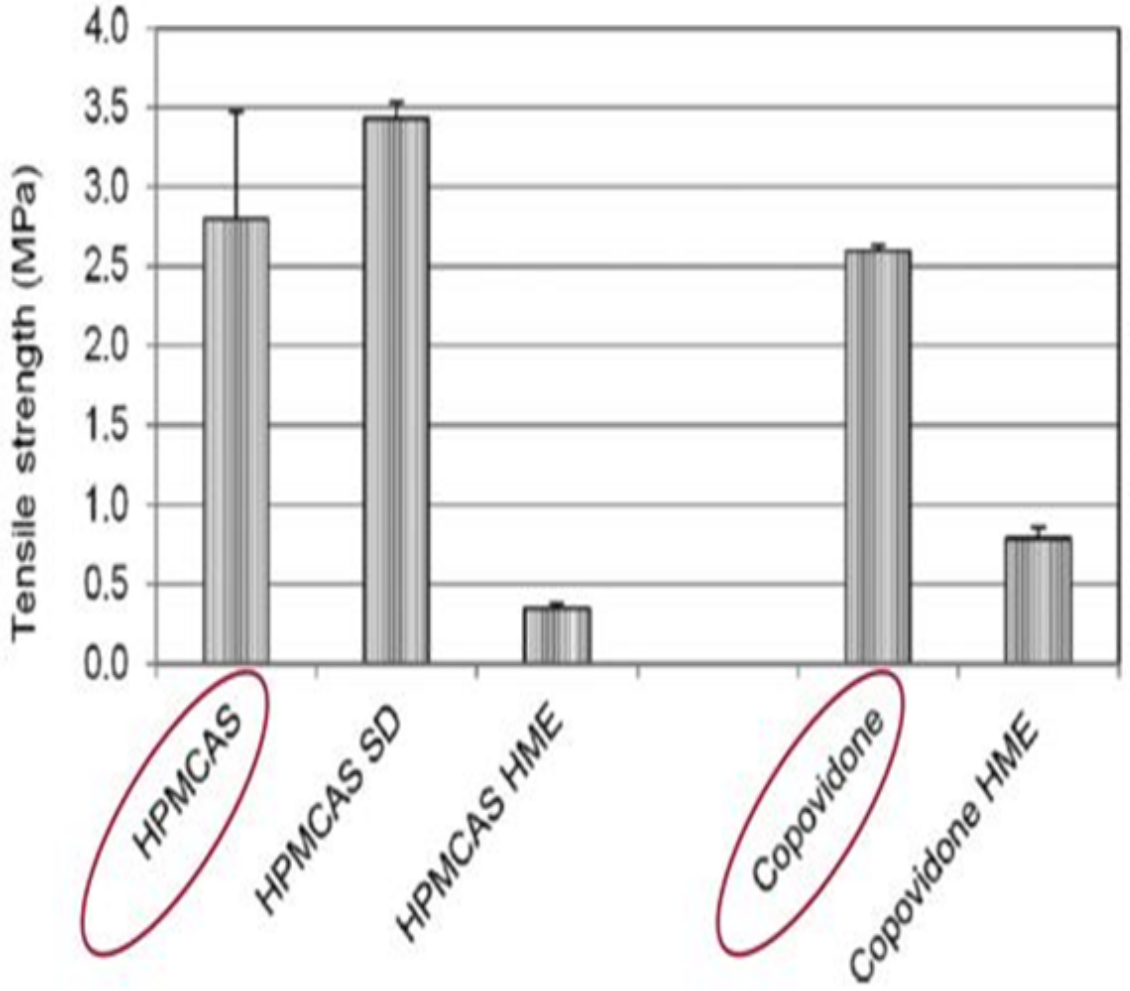
Predict critical mechanical properties of a formulation as a function of:

- Drug load
- Excipient selection and quantity
- Tablet solid fraction/compression pressure

Amidon GE. 2011. Oral Solid Dosage Forms. In Sinko P, editor Martin's Physical Pharmacy and Pharmaceutical Sciences, 6th ed.: Wolters Kluwer. p 563-593.

Process Parameters

Tensile strength, MPa, of pure material at solid fraction =0.85

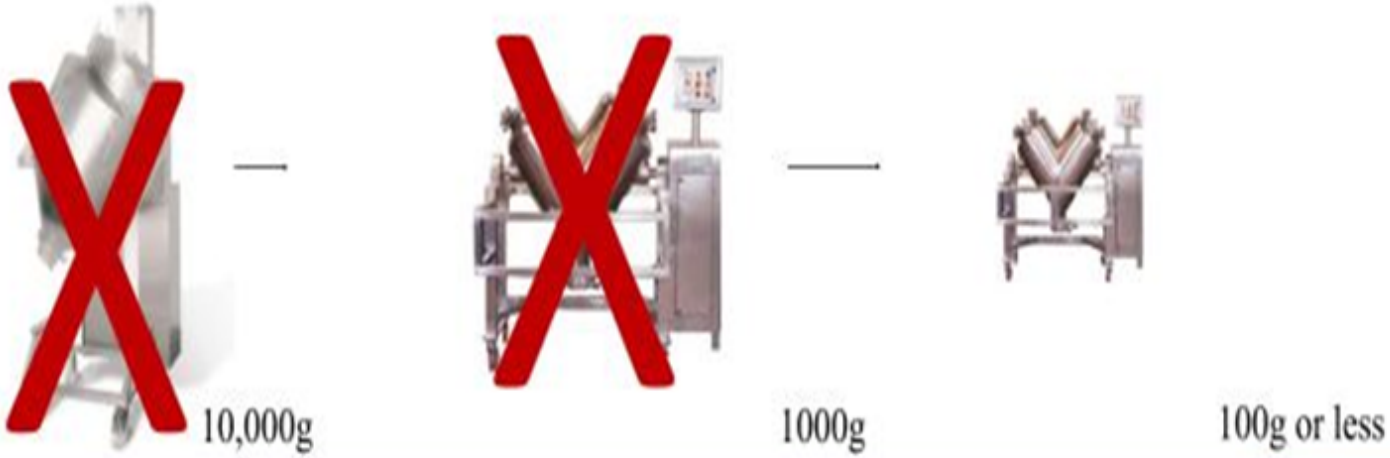


Iyer R, Hegde S, Zhang Y-E, Dinunzio J, Singhal D, Malick A, Amidon G 2013. The Impact of Hot Melt Extrusion and Spray Drying on Mechanical Properties and Tableting Indices of Materials Used in Pharmaceutical Development. Journal of Pharmaceutical Sciences 102(10):3604-3613.

We can more efficiently develop a tablet dosage form quickly with a smaller amount of drug

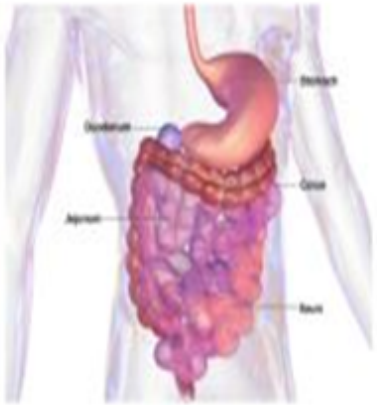
A more scientific approach to formulation development:

- Requires more data (physical, mechanical properties, processing impact) and more predictive relationships
- Improves efficiency of dosage form design and development by using predictive models and data
- Can use a material sparing approach: resource and time savings



Bridging In Vitro – In Vivo studies for Oral Products

GI Physiology is complex



Standard industrial product dissolution tests are not

Dissolution Testing: The Future

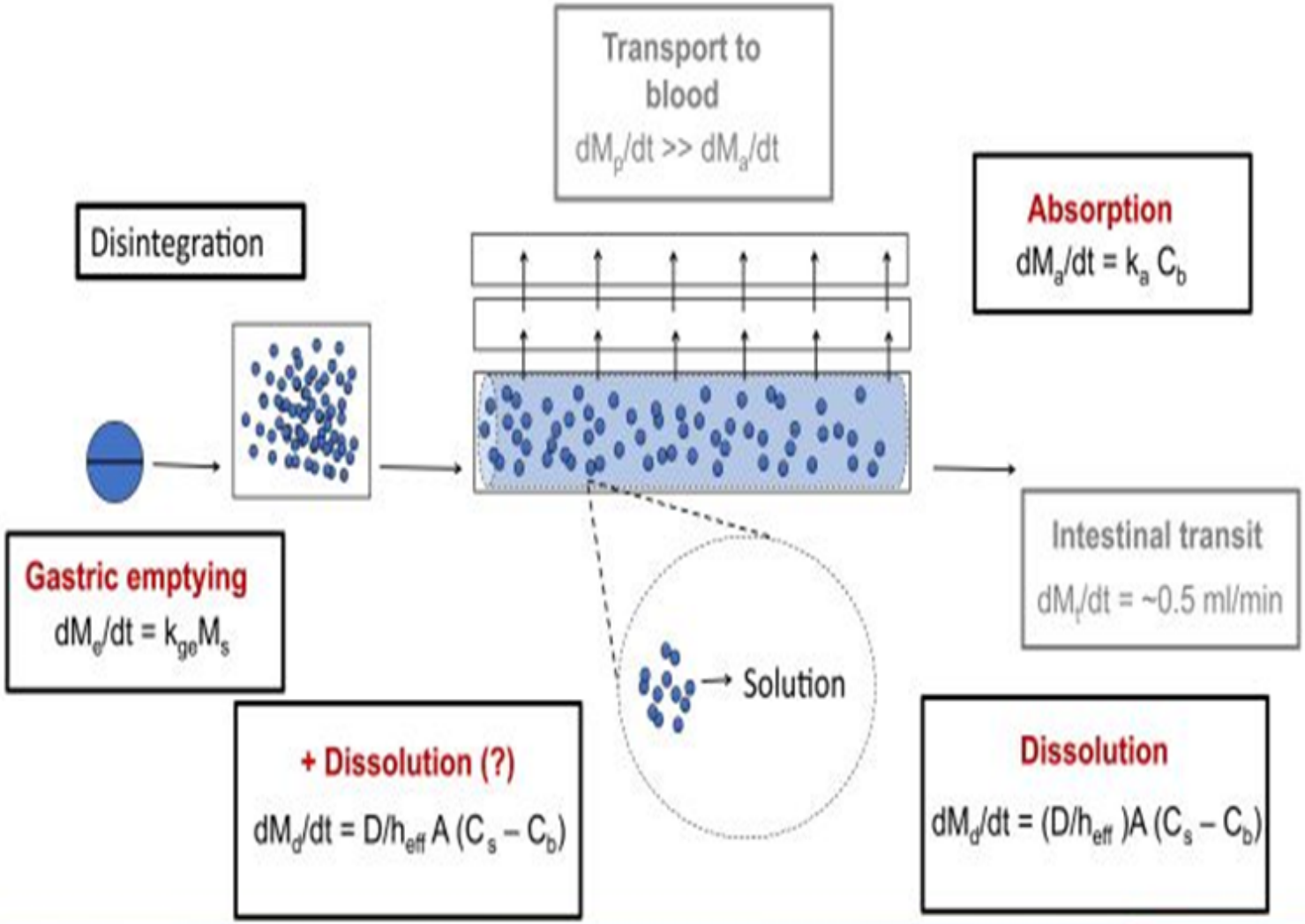
Need to transition to multiple dissolution methodologies for different purposes

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

In vivo Predictive Dissolution (IPD) should:

- Be physiologically relevant
- Consider drug properties: (acid, base, neutral)
- Consider dosage form properties (dose, applied technology)
- Address "Kinetic Properties"
  - 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: GIS, ASD, TIM)
    - Other (pH Dilution, etc)?
  - Integrate/consider absorption rate
    - Multiphase systems to simulate absorption: (eg: Biphasic, polymer membrane systems)

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

Bicarbonate Buffer: Reactions and Rates

$$CO_2(aq) + H_2O \overset{K_0}{\rightleftharpoons} H_2CO_3 \overset{K_1}{\rightleftharpoons} H^+ + HCO_3^-$$

$$K_a = K_0 K_1 \sim 10^{-6.04} \text{ or pKa } \sim 6.04 \qquad K_a = \frac{[H^+][HCO_3^-]}{[CO_2(aq)]}$$

$$CO_2(aq) + H_2O \underset{K_d}{\overset{K_h}{\rightleftharpoons}} H_2CO_3 \qquad H_2CO_3 \underset{K_r}{\overset{K_f}{\rightleftharpoons}} H^+ + HCO_3^-$$

$$K_0 = \frac{[H_2CO_3]}{[CO_2(aq)]}$$

$$K_0 = \frac{K_h}{K_d} \sim 10^{-2.6}$$

$$K_h \sim 0.1\ s^{-1}$$

$$K_d \sim 50\ s^{-1}$$

Residence time of CO_2 generated in aqueous boundary layer of dissolving particles is too short to react completely!

$$K_1 = \frac{[H^+][HCO_3^-]}{[H_2CO_3]}$$

$$K_1 = \frac{K_f}{K_r} \sim 10^{-3.5}$$

$$K_f \sim 8 \times 10^6 s^{-1}$$

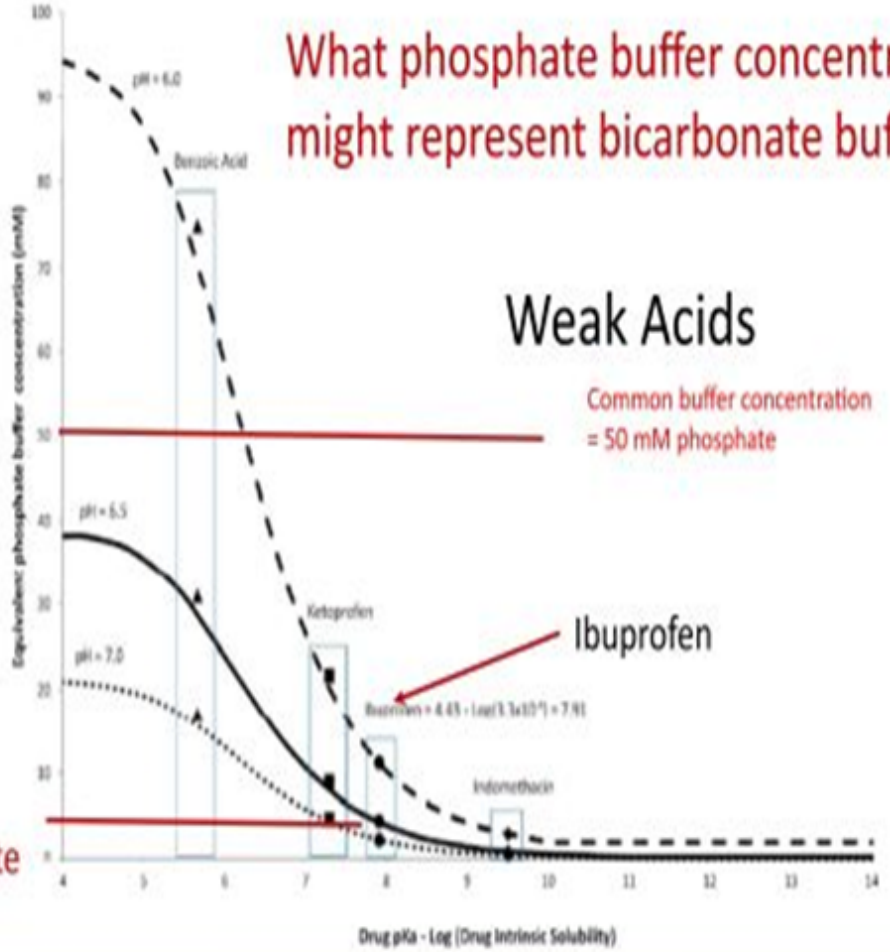
$$K_r \sim 5 \times 10^{10} s^{-1}$$

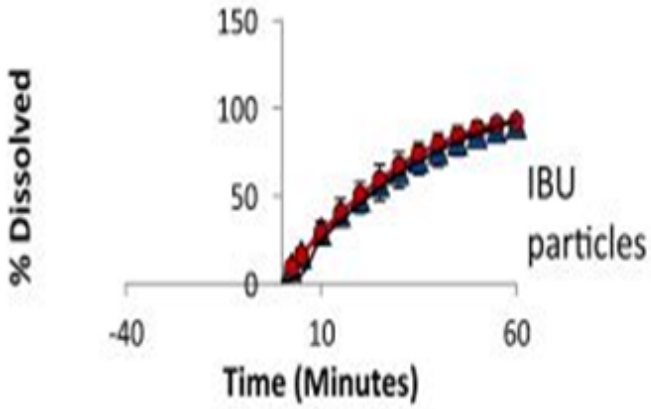
We know: GI buffer ≈15% CO_2 @ pH=6, 6.5, 7 (~10.4 mM HCO_3^-)

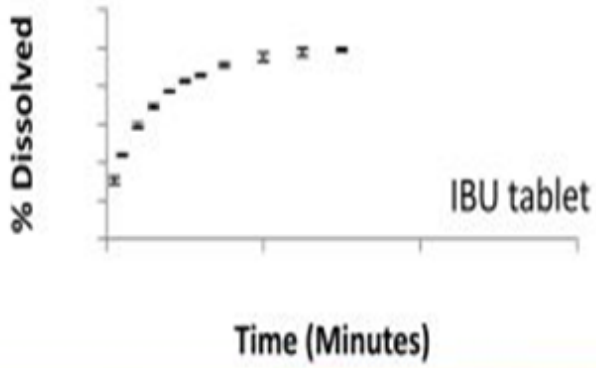
At the dissolving drug surface: $CO_2(aq) + H_2O \overset{k_d}{\leftarrow} H_2CO_3 \overset{K_1}{\rightarrow} H^+ + HCO_3^-$ $k_h \equiv 0$

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

What phosphate buffer concentration might represent bicarbonate buffer?





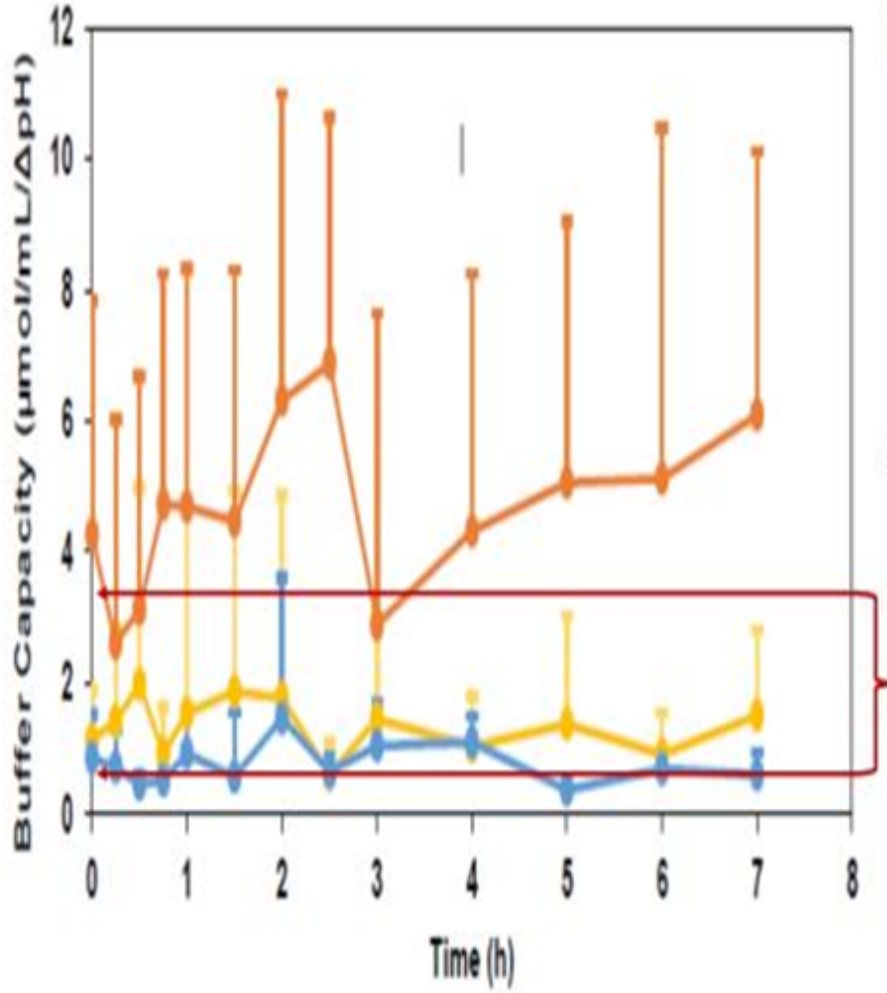


Bicarbonate Buffer Concentration and Buffer Capacity as a function of pH and $\%CO_2$

Bicarbonate Buffer Concentration (mM), Buffer Capacity in parentheses (mmol H+ /L/pH)						
	% CO_2					
pH	5%	10%	15%	20%	40%	60%
5.5	0.19	0.381	0.57	0.76	1.52	2.29 (0.61)
6	0.6	1.2	1.81	2.41	4.82	7.23
6.5	1.9	3.81 (2.1)	5.71 (3.1)	7.62 (4.2)	15.23	22.85
7	6.02 (1.9)	12.04	18.07	24.1	48.17	72.26
7.5	19.04 (2.5)	38.08	57.13	76.17	152.34	228.51

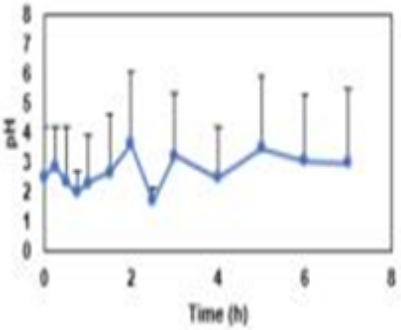
50 mM phosphate buffer capacity at pH 6.5 = ~25 mmol H^+ /L/pH

In Vivo Buffer Capacity: Humans Fasted State Sampled through GI Tube

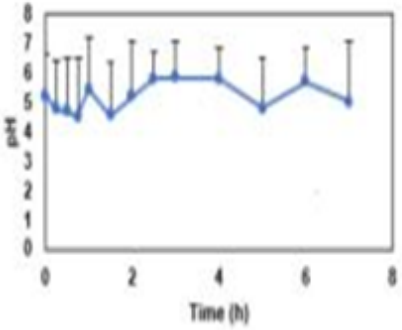


Fasted

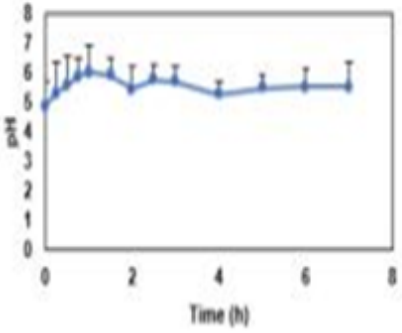
Stomach



Duodenum



Jejunum



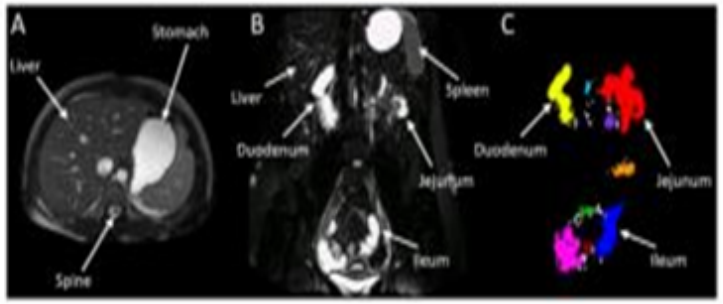
Buffer Capacity Stomach — Buffer Capacity Duodenum — Buffer Capacity Jejunum

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).

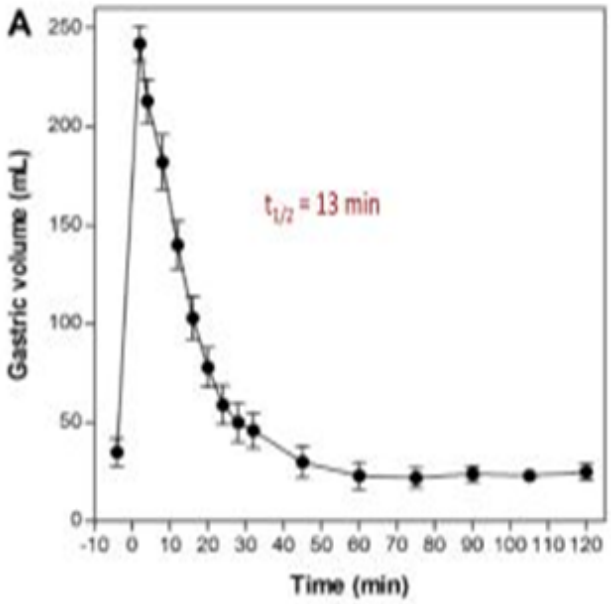
Intestinal Water Content (by MRI)

Fasted state
240 mL water dose

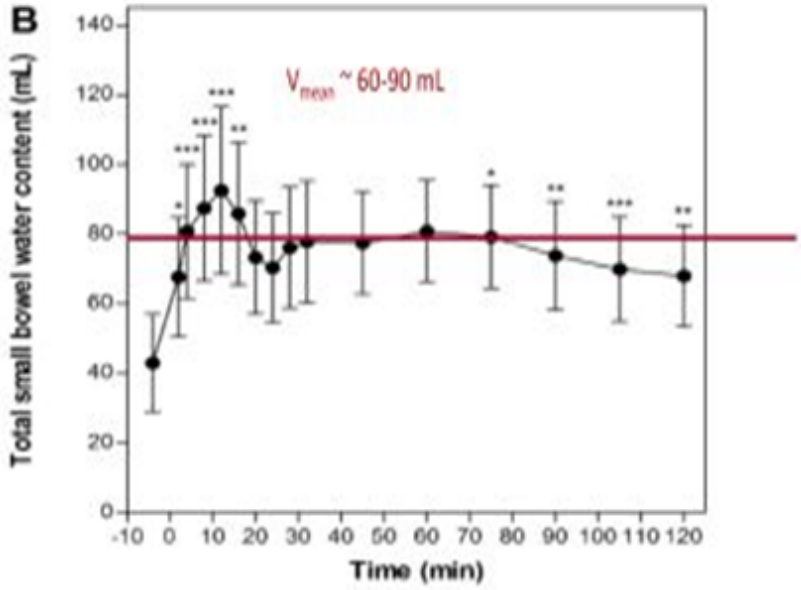
MRI in healthy volunteers



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

Physiologically relevant conditions we now know better… and can integrate into dissolution test conditions

- Stomach emptying rate ($t_{1/2}$ ~ 13 min) variable (complicated)
- Buffer concentration low, 5-15 mM bicarb (lower for PO 4)
- Buffer type: bicarbonate (equivalent phosphate)
- pH (stomach: 1-5, duodenum: 3-6, jejunum: 5-7)
- Fluid volume (60-90 mL in small intestine)

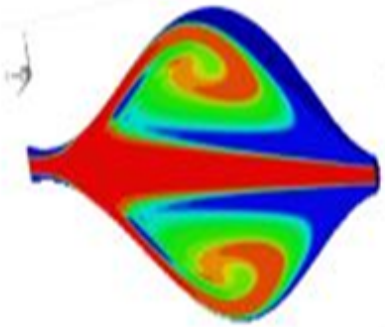
What about:

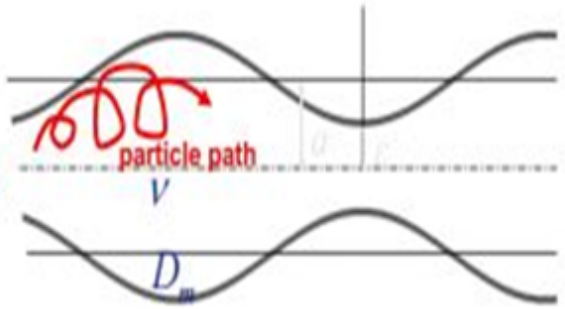
- Hydrodynamics?
- Absorption?

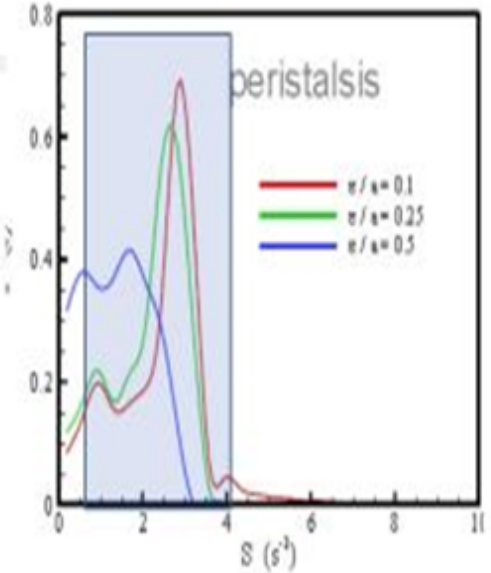
Hydrodynamic Parameters that Govern In Vitro and In Vivo Dissolution

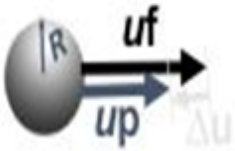
(Jim Brasseur (UColorado) Computational Fluid Dynamics

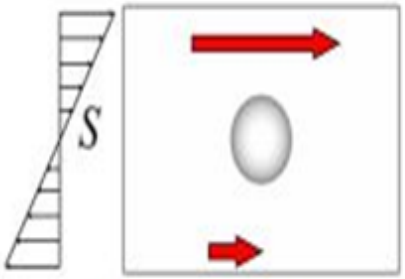
Model Intestinal fluid flow



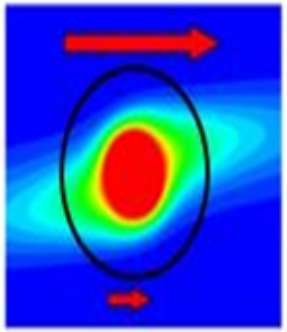






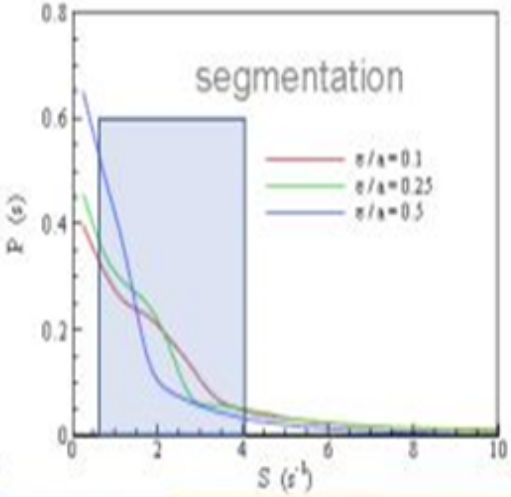


Convection



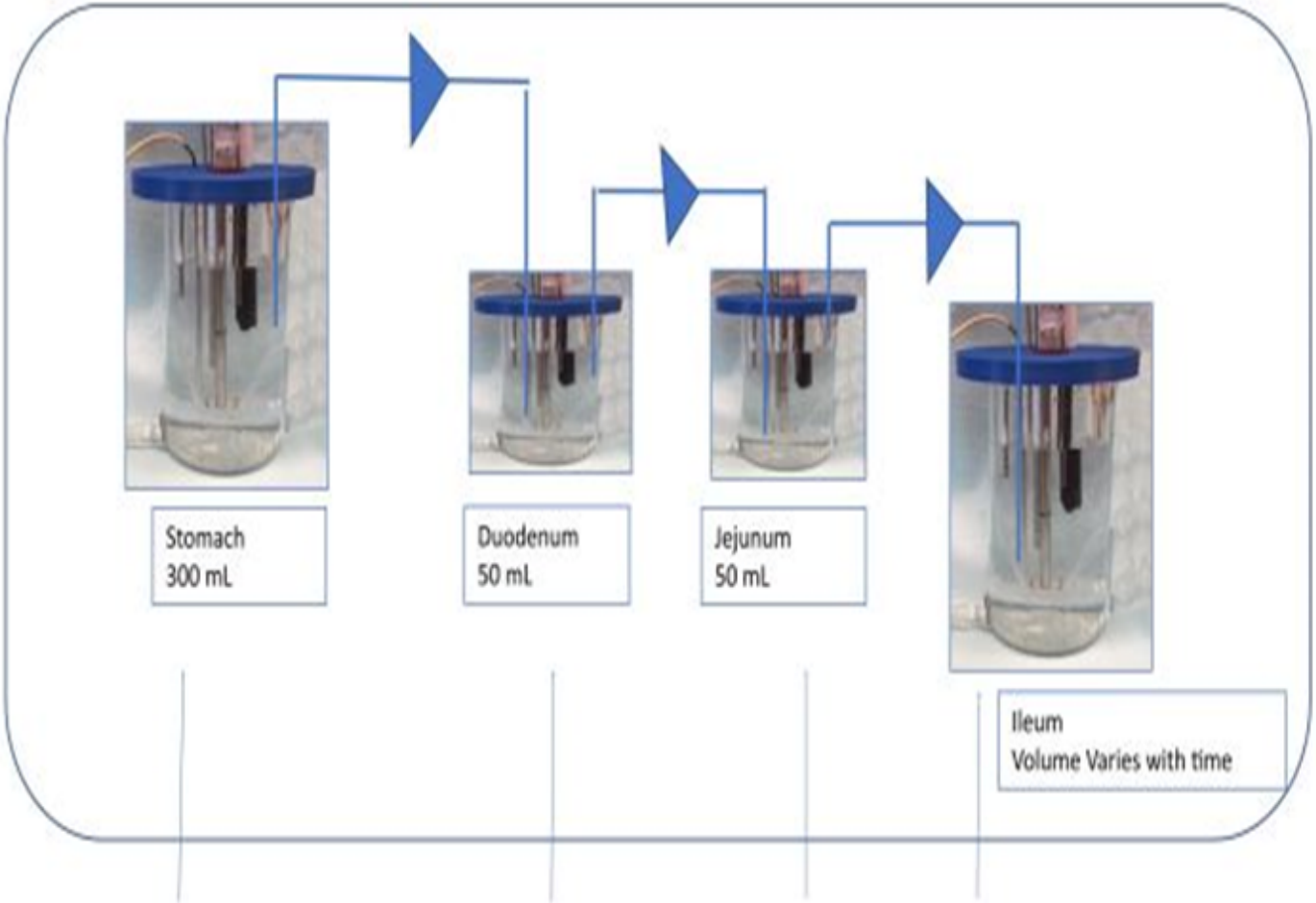
Shear

In vivo shear rates ~ 1 -10 s^{-1}



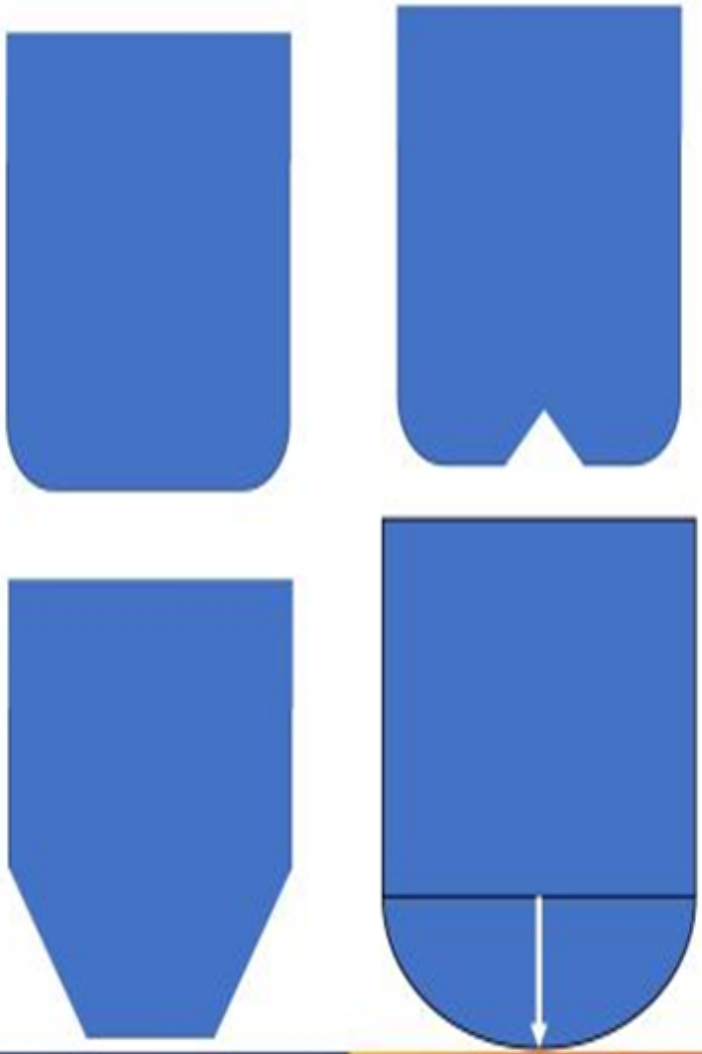
Simulations: Brasseur, Wang , Behafarid

Modular Gastrointestinal Simulator (GIS)



Realistic volume, pH, buffer capacity, hydrodynamics (to extent possible)

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

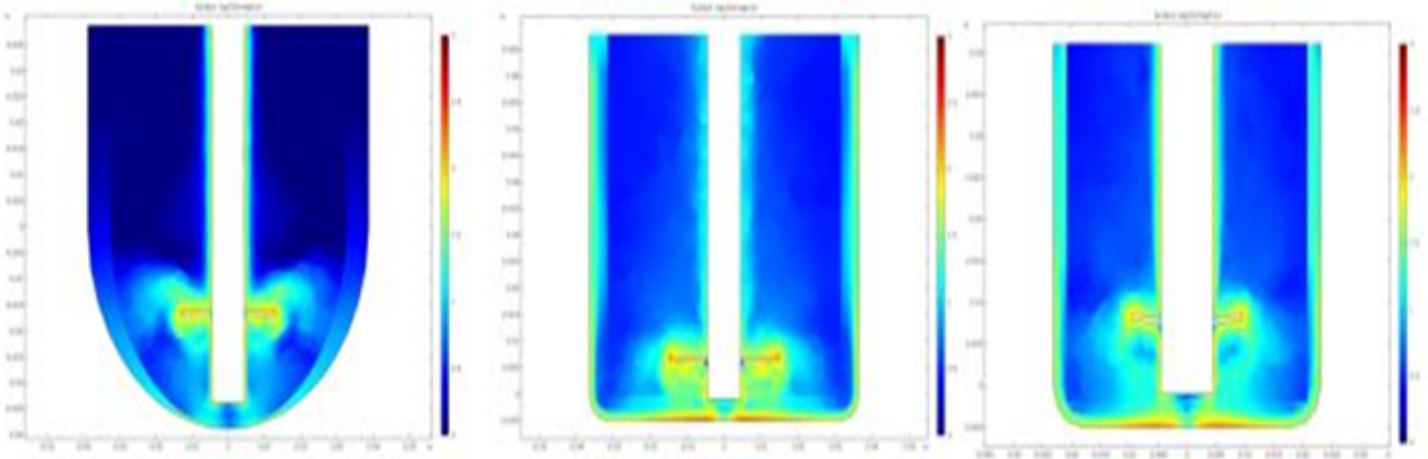


Images via Google Images
Graphic via Thermopedia.com "Mixers"

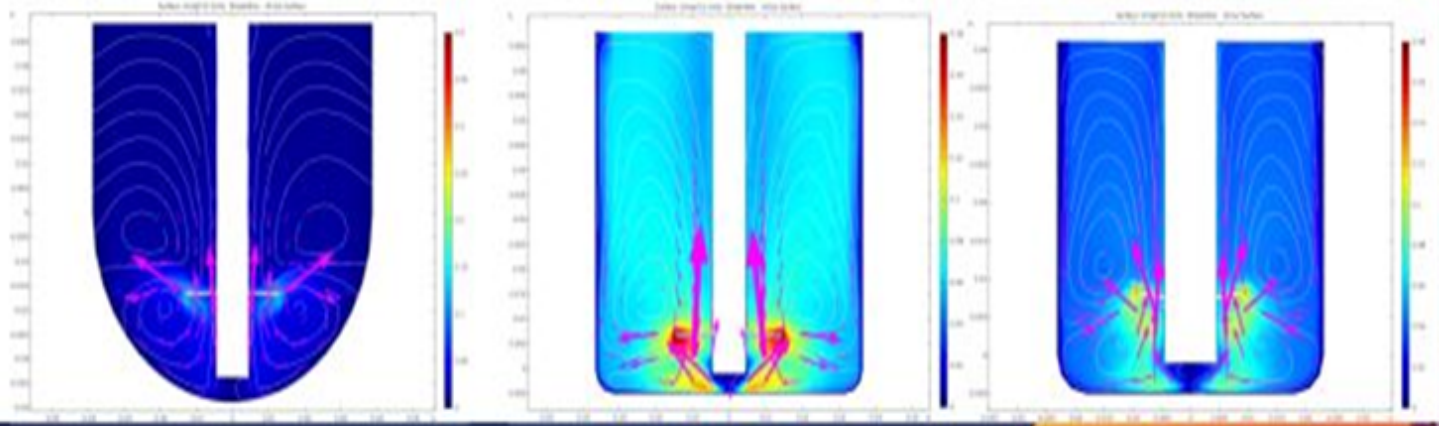
Hydrofoil and vessel design examples. Goal: Achieve assess/achieve shear rates

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

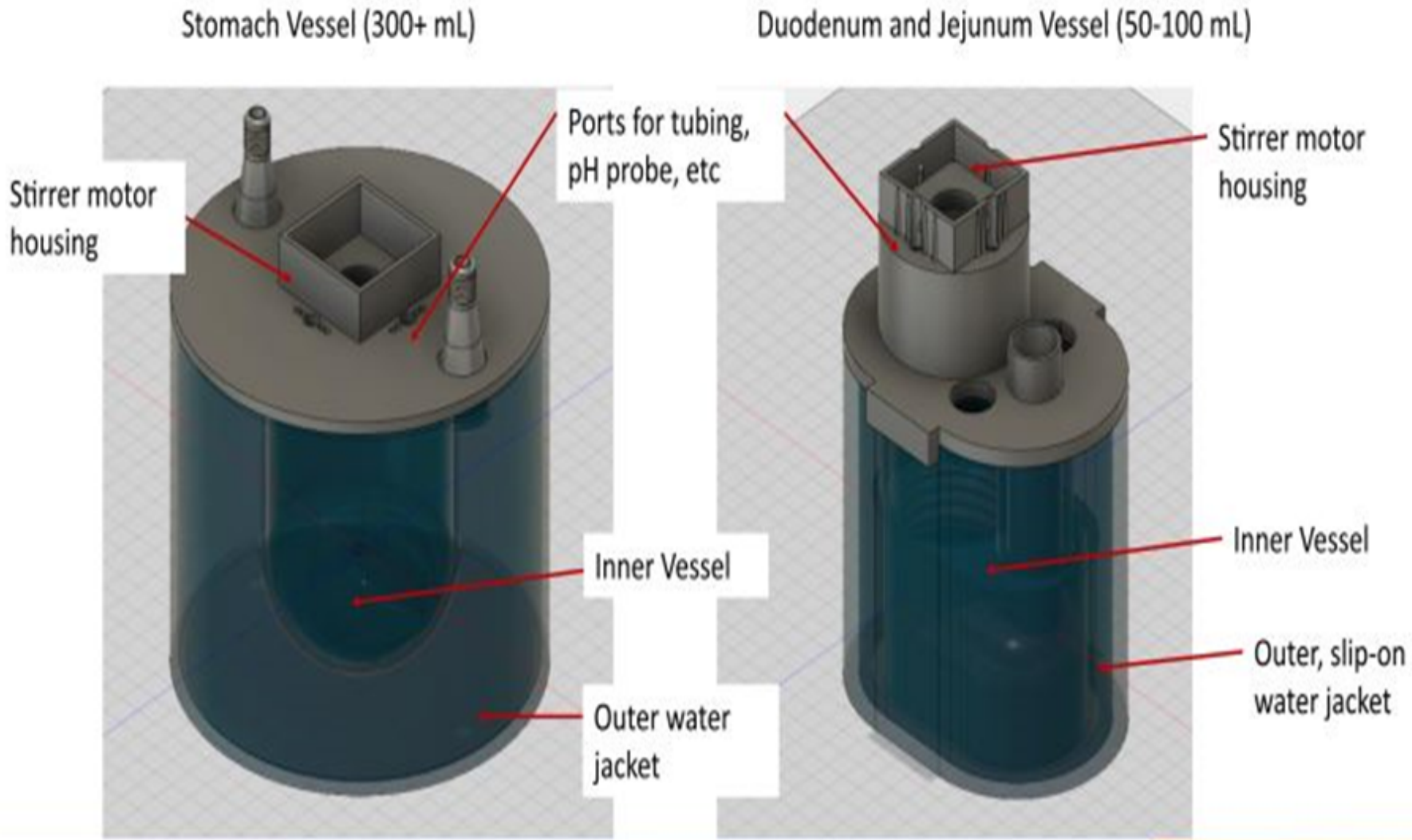
Log(shear rate)
Log[s^{-1}]



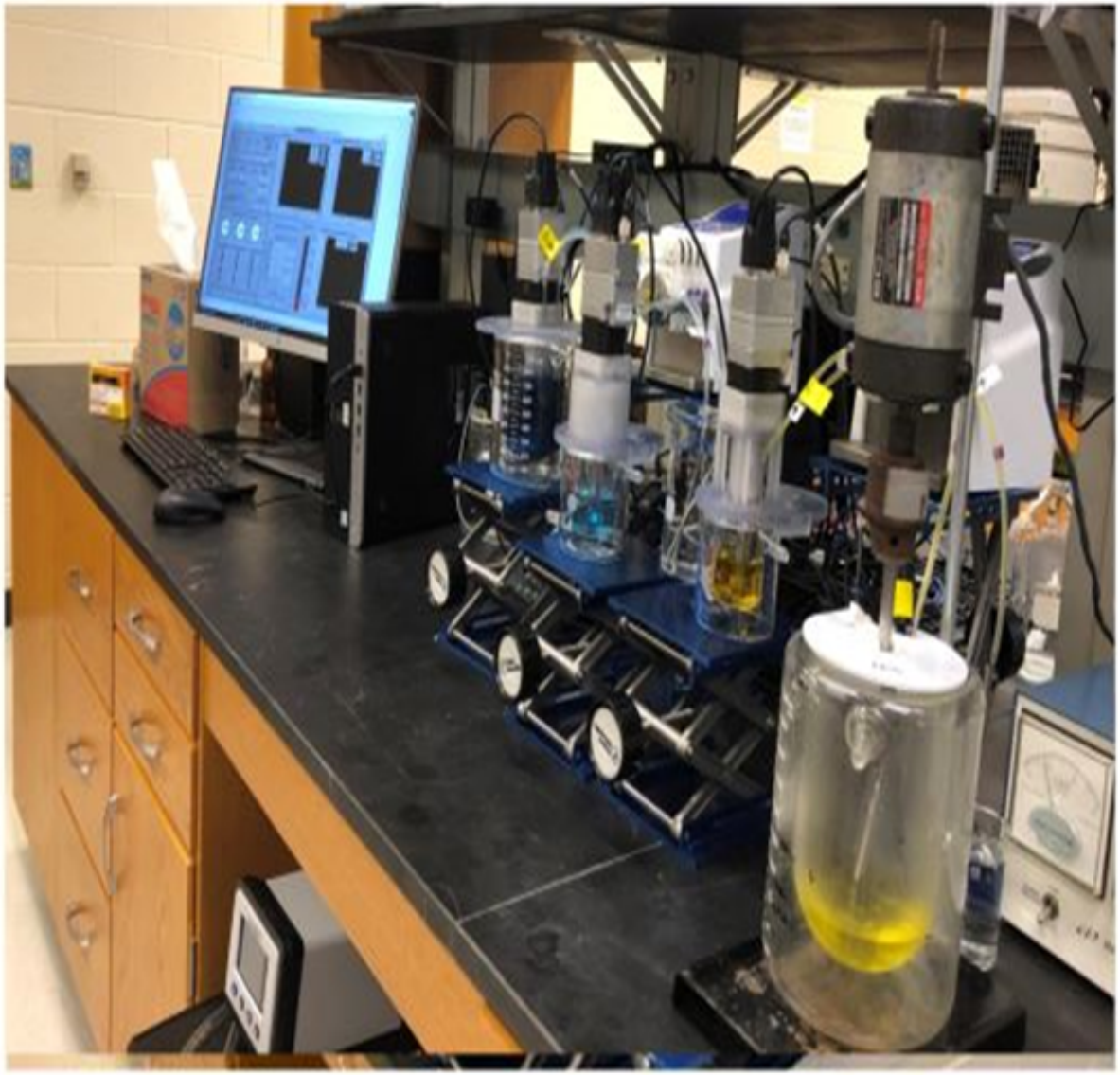
Velocity Profile
[ms^{-1}]



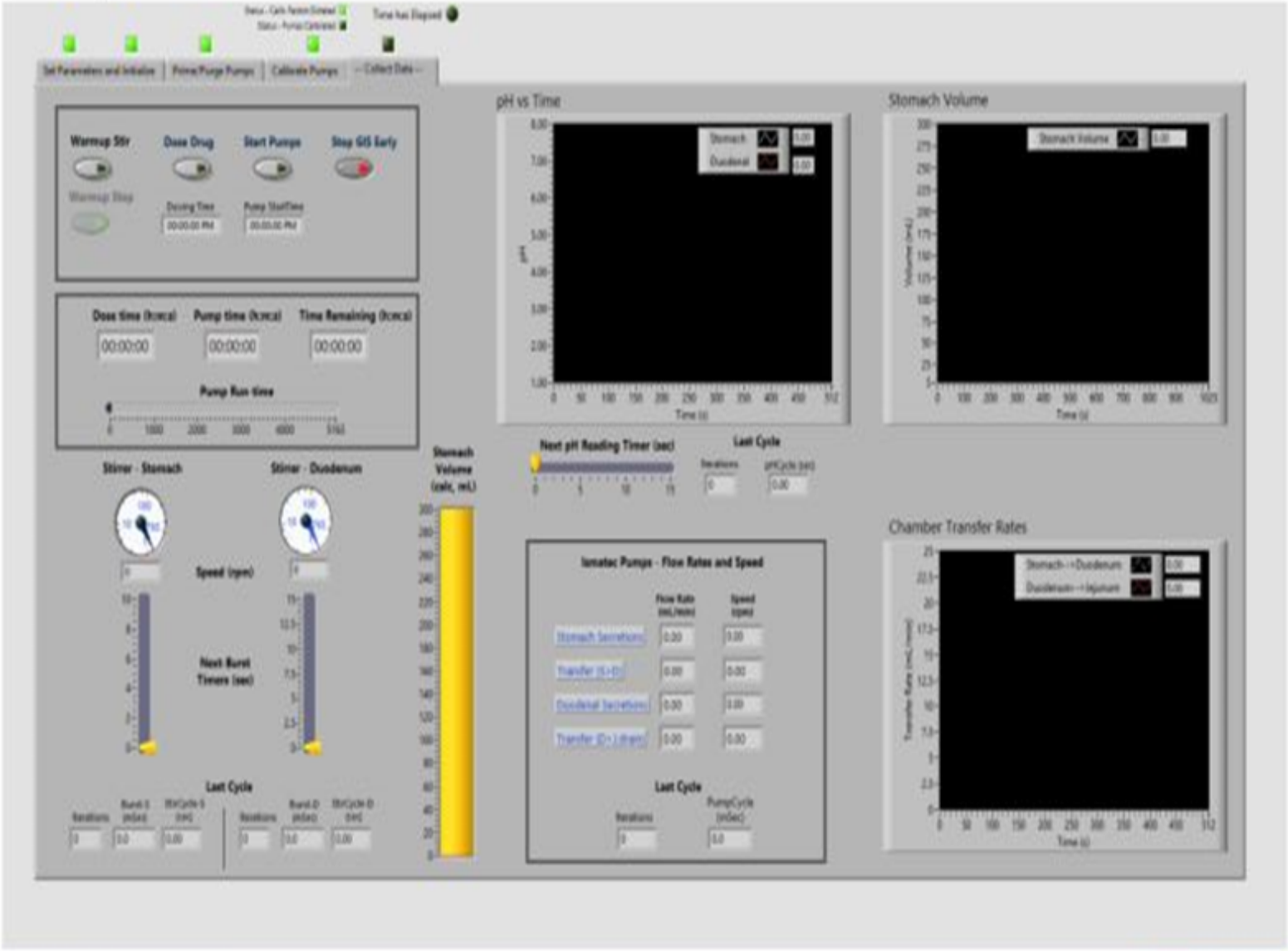
GIS Modular Setup (3D designed and printed) with inner dissolution vessel and outer water jacket



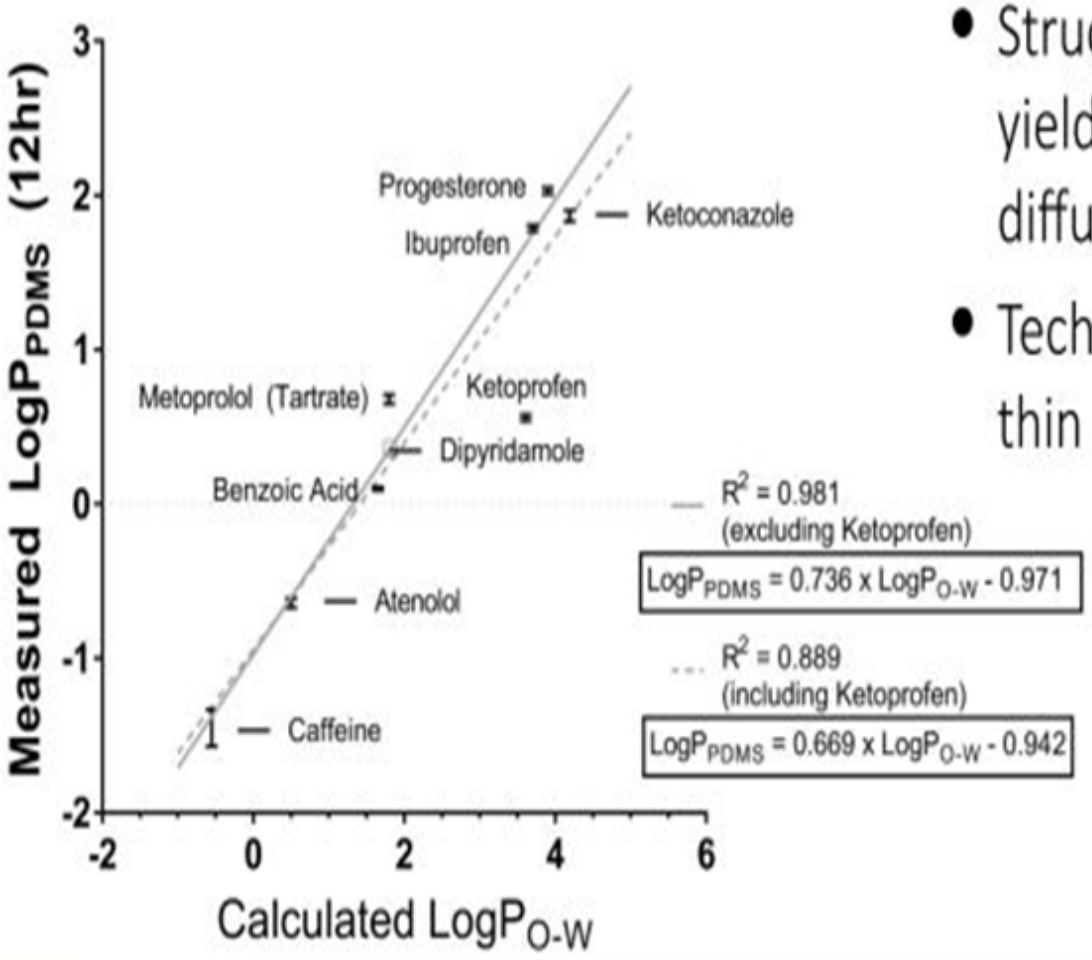
Gastrointestinal Simulator: GIS 2.0



Graphical User Interface

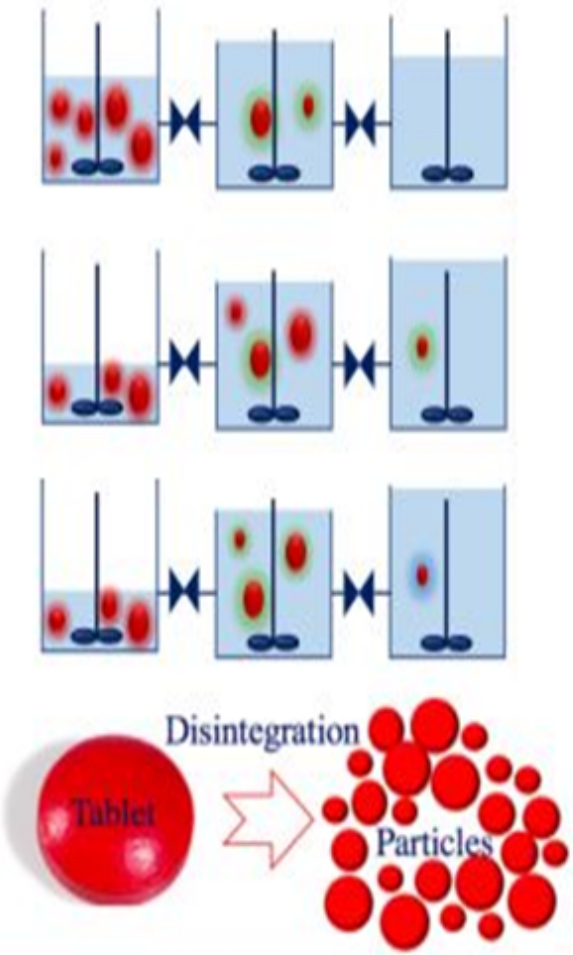


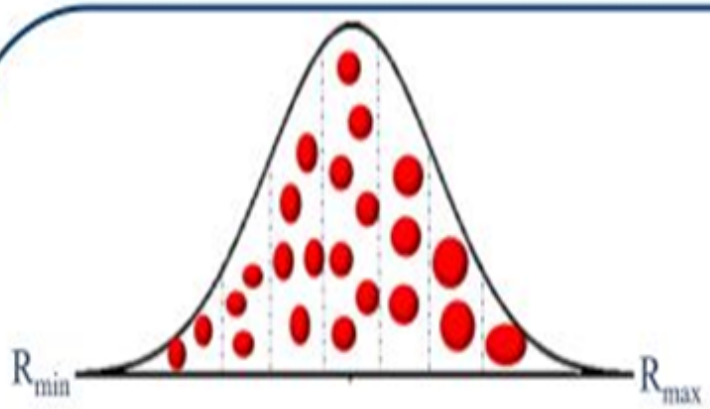
Simulating Absorption: Polydimethyl siloxane (PDMS) Membrane to simulate Absorption:



- Structure based prediction can yield PDMS partition and diffusion coefficients
- Technology available to make thin membranes (<10 um)

Mass Transport Analysis of GIS





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

$C_s(t)$: Solubility

$C_b(t)$: Bulk concentration

v_m: Molar volume of the drug

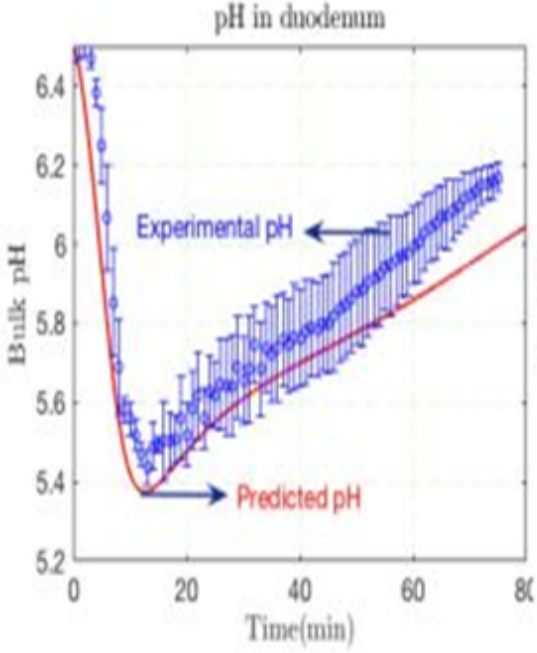
D: Diffusion coefficient of drug molecules

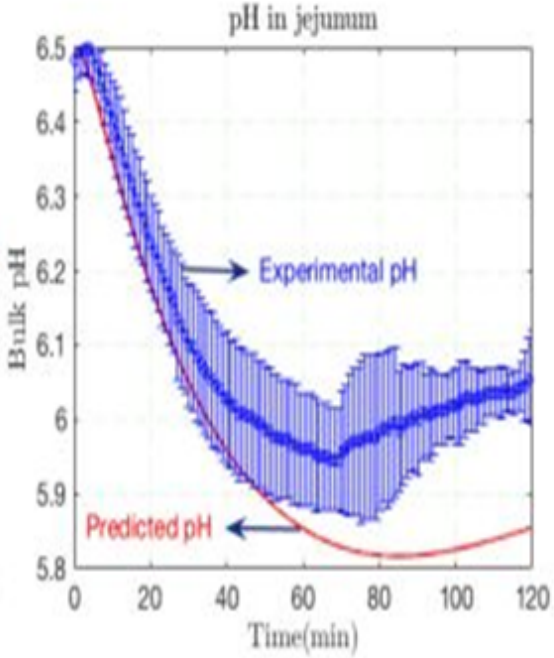
R_j: Radius of particle

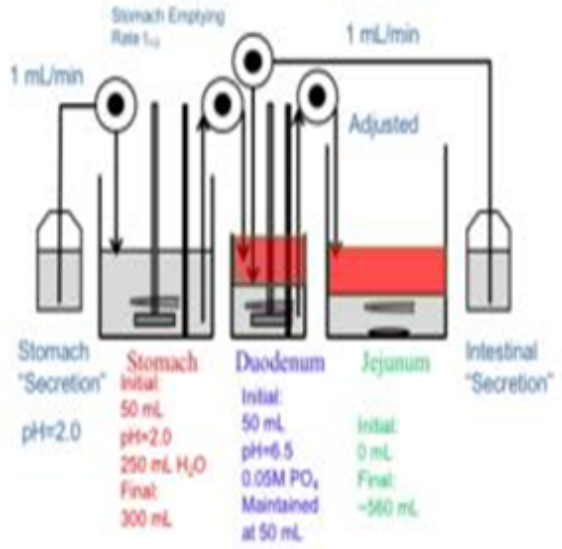
$$Sh = 1 + \Delta_{confinement} + \Delta_{shear}$$

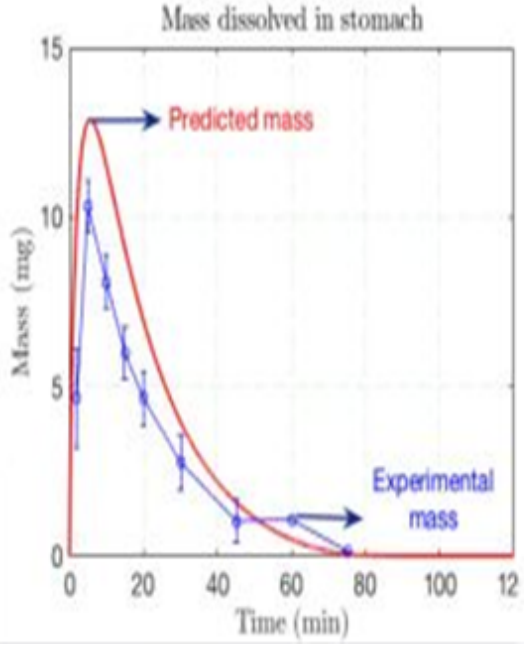
Prediction vs. Experiments for 800 mg Ibuprofen Tablet in GIS

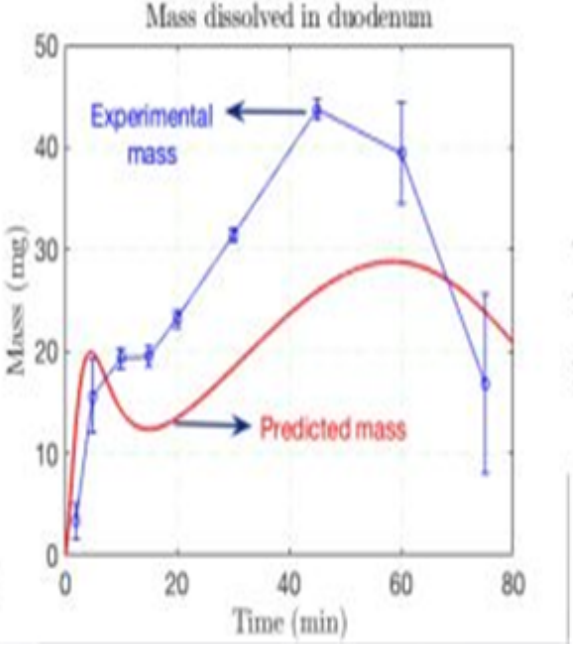
$t_{1/2} = 13\ min$

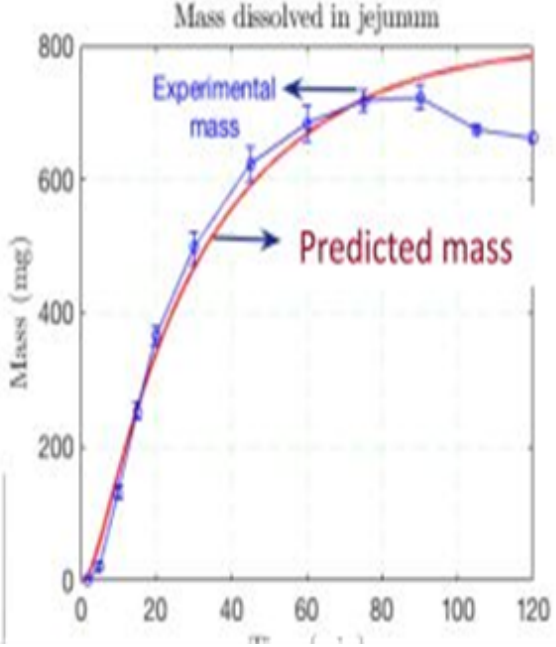












Conclusions

- The properties of oral tablet formulations are "predictable" and can be more scientifically designed and developed.
- We are learning more and more about the in vivo environment of the GI tract (Gordon Amidon and others have spoken about this at this meeting)
- We are working to integrate physiologically relevant "conditions" into dissolution equipment and experiments (Gastrointestinal Simulator (GIS))
- GIS tests have demonstrated enhanced discrimination in dissolution profiles of a variety of drugs and dosage forms (
  - Very much a work in progress! See published research with more to come.

We continue to move away from "Guided Empiricism"* toward scientific formulation development, characterization, and performance.

* Everett Hiestand (1930-2018)

Work to date: Human GI and GIS-related publications from U-MI labs (2010-2018)

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Acknowledgments

- Deanna Mudie, PhD — Lonza (Bend Research)
- Brian J. Krieg, PhD — Perrigo Pharmaceuticals
- Arjang Talattof, PhD — Scape Technologies Ltd
- Hao Xu, PhD — Postdoctoral Fellow, Abbvie
- Jozef Al-Gousous — Postdoctoral Fellow, U-M
- Bart Hens — Postdoctoral Fellow, U-M
- Patrick D. Sinko — Graduate Student
- Nicholas Job — Graduate Student
- Niloufar Salehi — Graduate Student
- Pirinka Georgiev — Undergraduate BSPS student
- Meagan Dean — Undergraduate BSPS student
- Sarah Harris — Undergraduate BSPS student
- Yue Yuan — Undergraduate BSPS student
- Troy Halseth — Undergraduate BSPS student
- Ava Dalton — High school student
- Hiro Tsume, PhD — Research Scientist, U-M
- Kazuki Matsui, PhD — Visiting Scientist
- Susumu Takeuchi, PhD — Visiting Scientist
- Naoto Igawa — Visiting Scientist
- Gordon Amidon, PhD — Professor, U-M
- Randy J. Wald RPh — GIS Interface, consultant

Financial Support Provided by:

- Chingju Wang Sheu Graduate Student Fellowship
- Everett N. Hiestand Graduate Student Fellowship
- Abbott 2008-2011
- Abbvie 2015-2018
- USP Fellowship 2010-2012
- AstraZeneca 2012-2013
- FDA Contract HHSF223201310144C: 2013-2016
- FDA Contract HHSF223201510157C: 2016-present
- NIH R01 GM107146 2014-2018

Questions

Contact: geamidon@med.umich.edu