FY 2017 Generic Drug Research
FDA Public Workshop
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Stochastic Frameworks for Variability in Oral Dissolution-Absorption and Predictability

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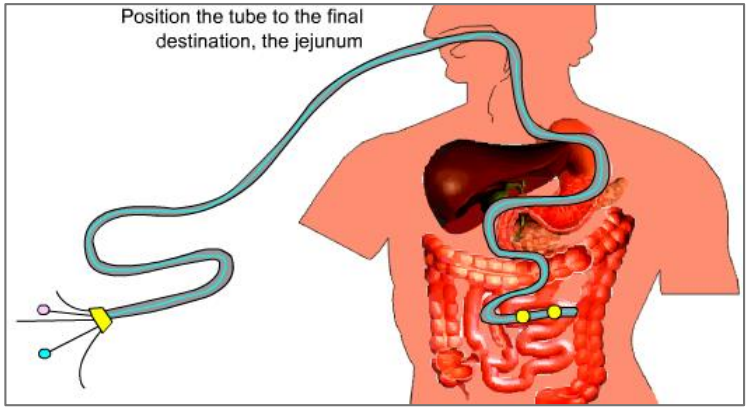
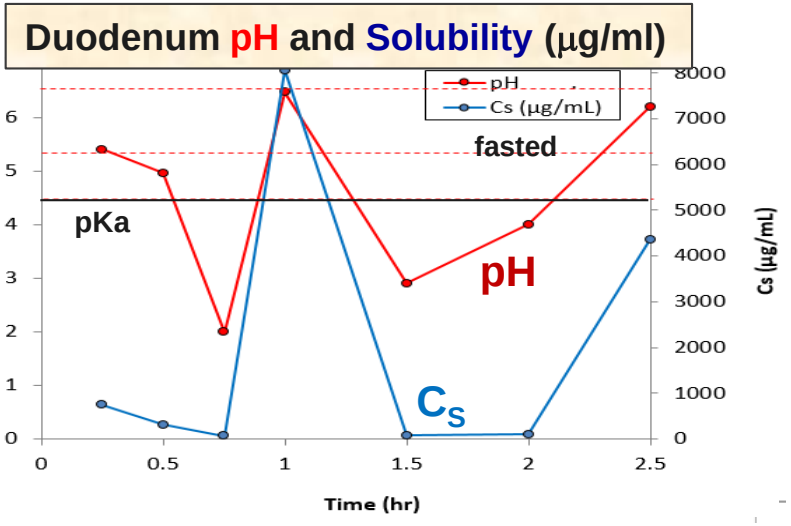
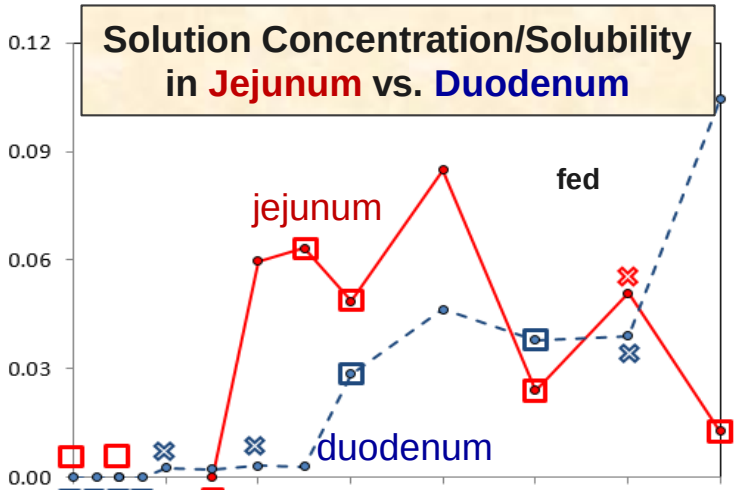
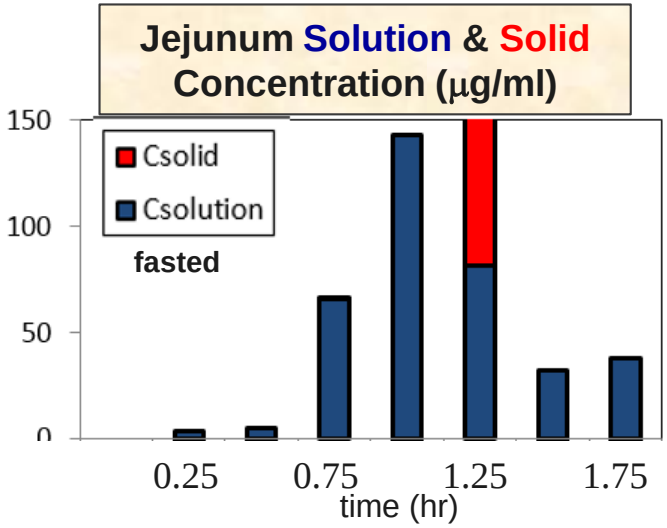
Variability in Gastro-Intestinal Drug Absorption Processes

From Amidon, *et al.* University of Michigan

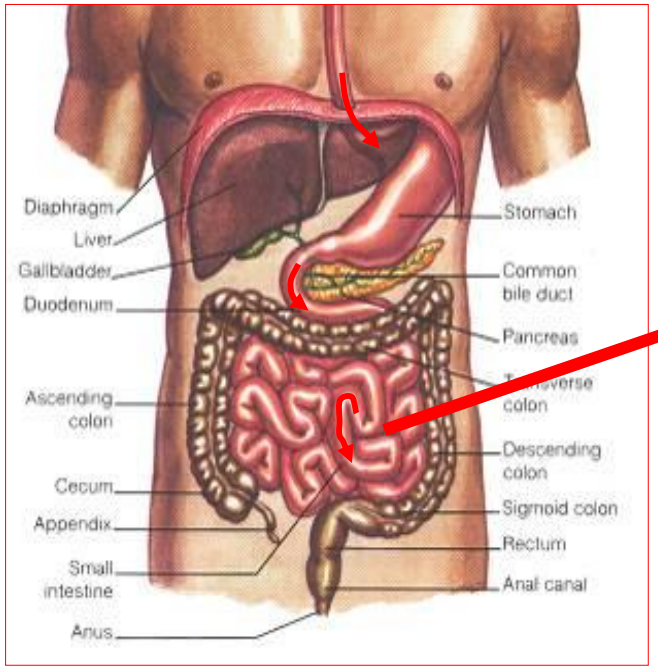






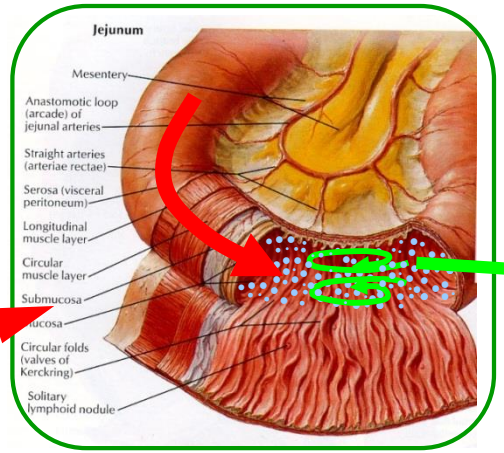


Variability from Gastro-Intestinal Motility



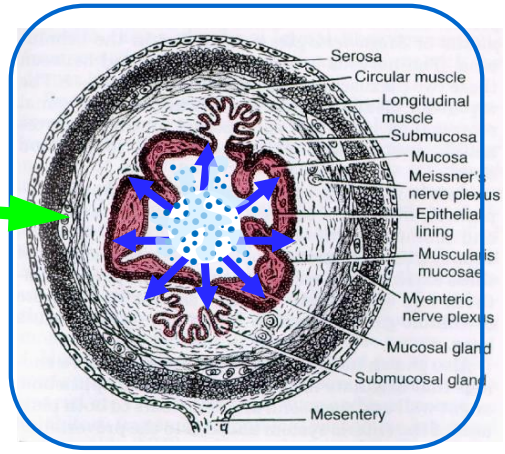
Transport of Drug Particles along Intestines:

MOTILITY-DRIVEN HYDRODYNAMICS



Dissolution + Mixing, Transport of Drug Molecules to Intestinal Walls:

MOTILITY-DRIVEN



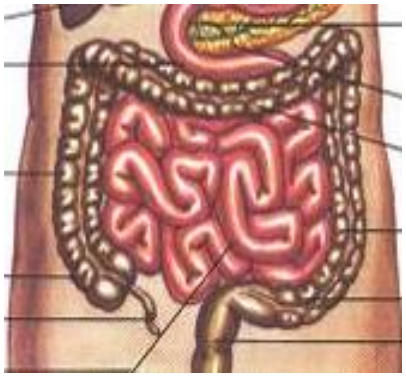
Absorption of Drug Molecules across Mucosal Epithelium:

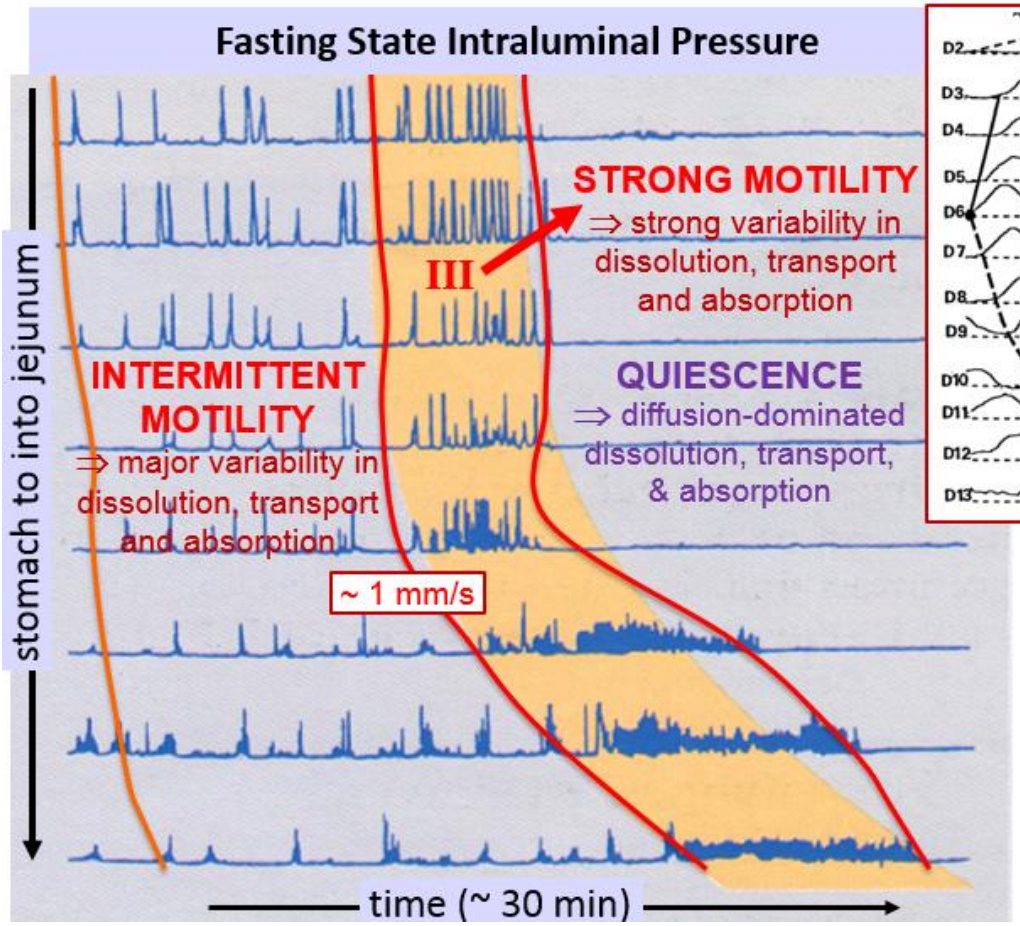
ABSORPTION RATE driven by LUMINAL MIXING RATE

MIXING RATE DRIVEN BY MOTILITY

Complexity in GI Motility Patterns Drive High Variability in Absorption

TRANSPORT of Drug Particles along the Intestinal Tract:
MOTILITY-DEPENDENT

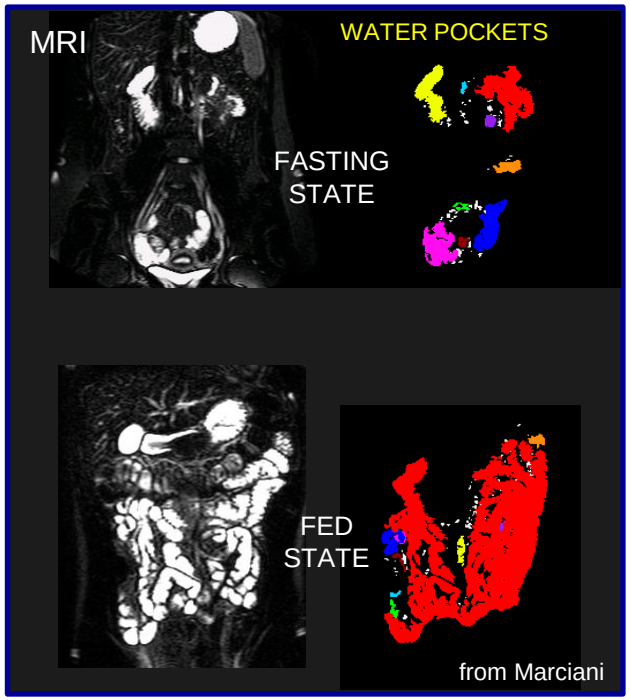




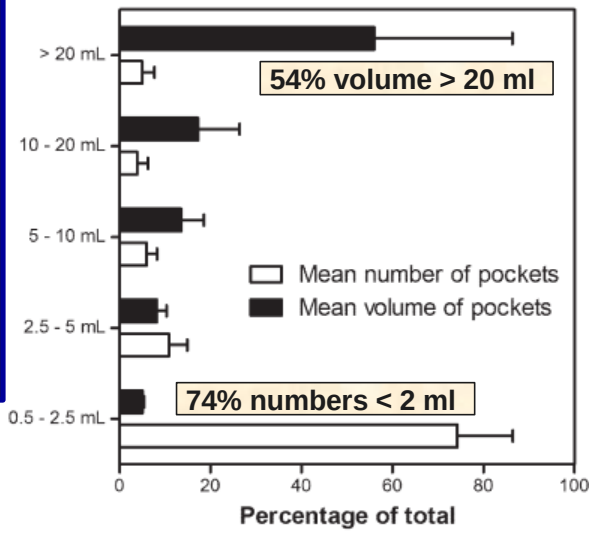
Liquid Volume Content in Small Intestine Pockets is Highly Variable

High Levels of Variation in Small Intestine Pocket Volume:

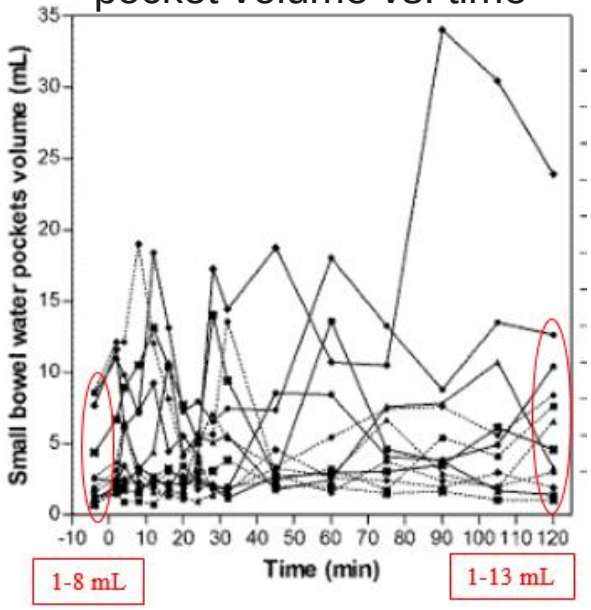
- in time
- spatially along the gut
- among subjects



distribution of pocket volumes



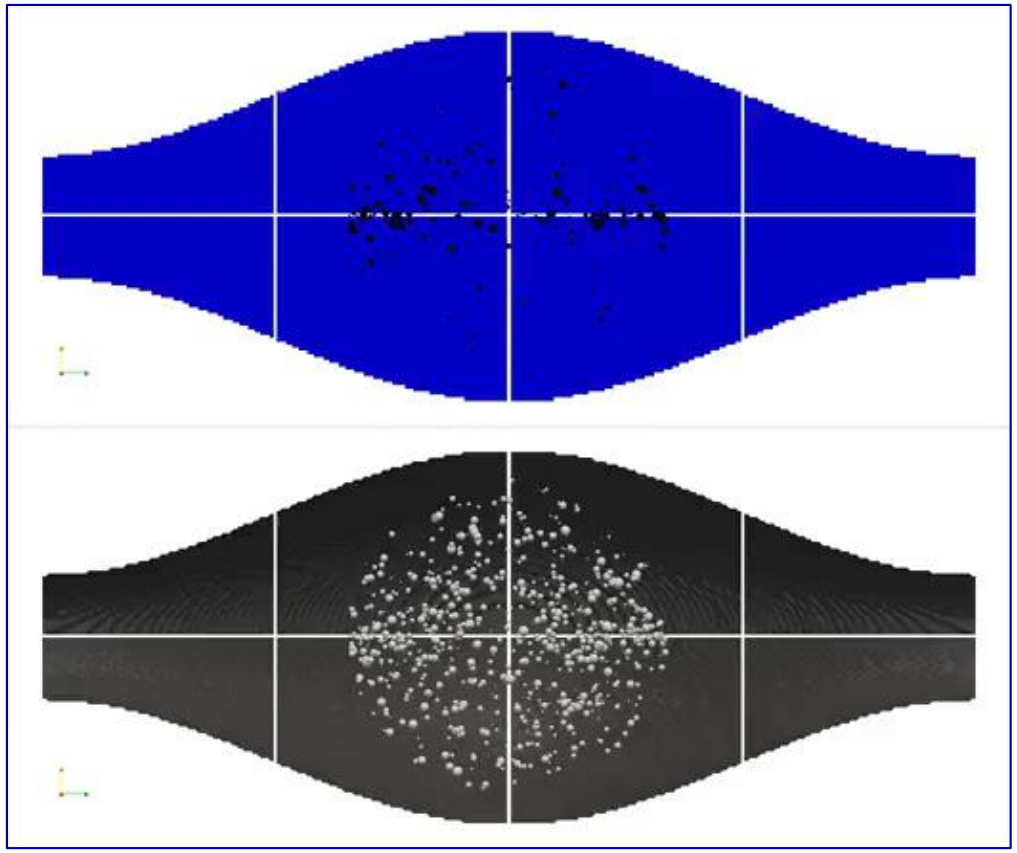
pocket volume vs. time



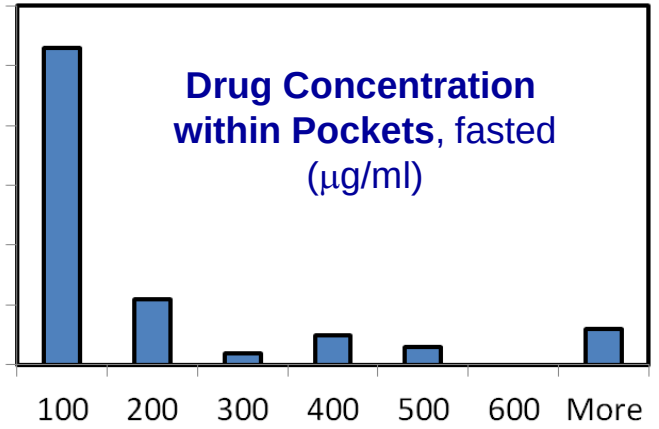
Quantification of Gastrointestinal Liquid Volumes and Distribution Following a 240 mL Dose of Water in the Fasted State

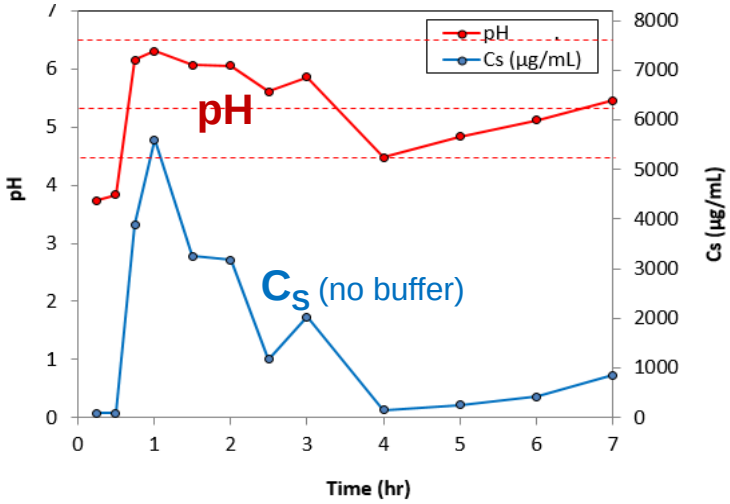
Deanna M. Mudie,[†] Kathryn Murray,[‡] Caroline L. Hoad,[‡] Susan E. Pritchard,[‡] Martin C. Garnett,[§] Gordon L. Amidon,[†] Penny A. Gowland,[‡] Robin C. Spiller,[∥] Gregory E. Amidon,[†] and Luca Marciani*[,∥]

Intestinal Transport, Dissolution and Absorption is **Highly Variable**



Computational Fluid Dynamics
simulations: Brasseur & Behafarid.





***in vivo* data**: Amidon *et al.*

Stochastic Modeling Frameworks

High levels of variability are inherent in the physiological and mechanical function of the gut

⇒ Inherently high levels of variability in drug transport, dissolution and absorption *in vivo*

⇒ There is a need for new first-principles-based Probabilistic Mathematical Modeling Frameworks

- **that incorporate variability in GI physiology and function**
- **that predict variability (standard deviation, distributions, etc.)**
- **for application within *in silico* PBPK Prediction**