Mechanistic Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence (BE) Evaluation

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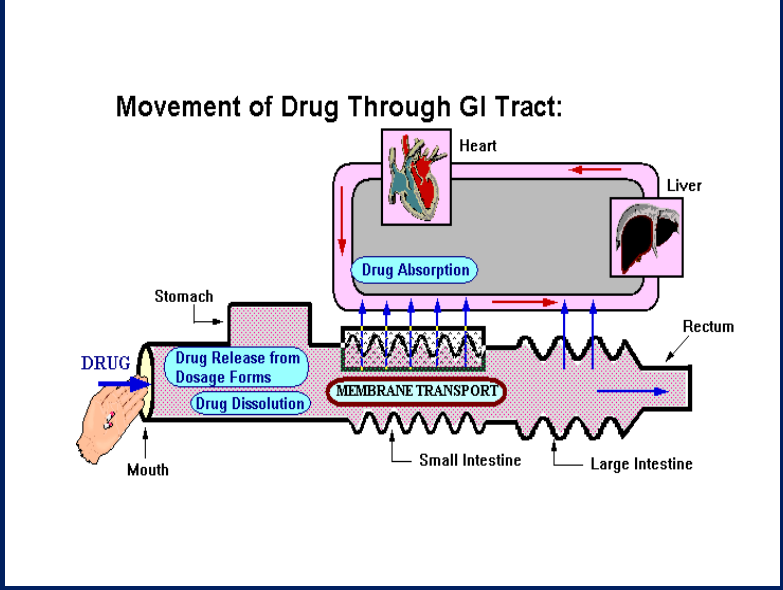
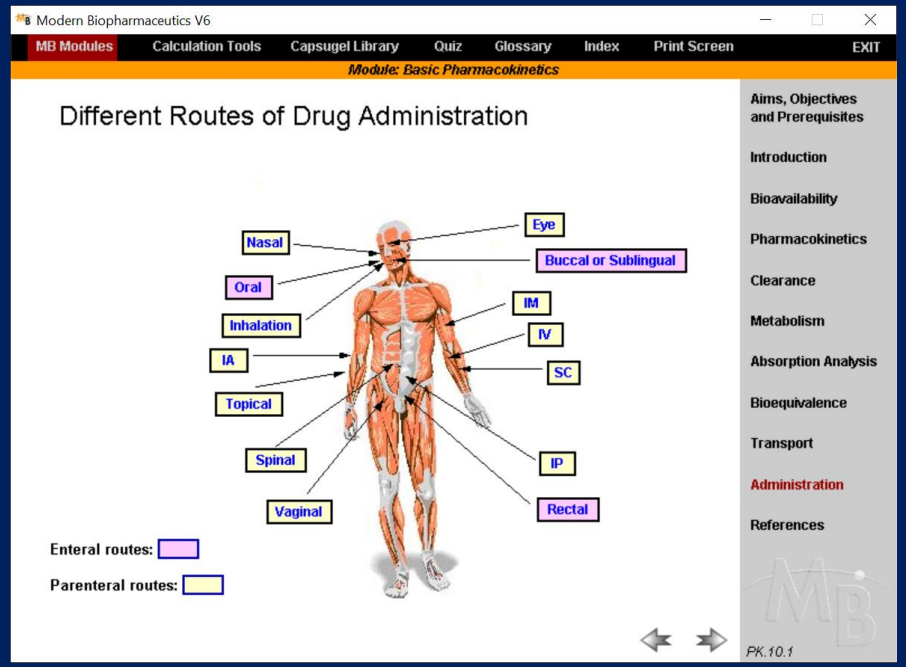
FDA Workshop: May 19,2016

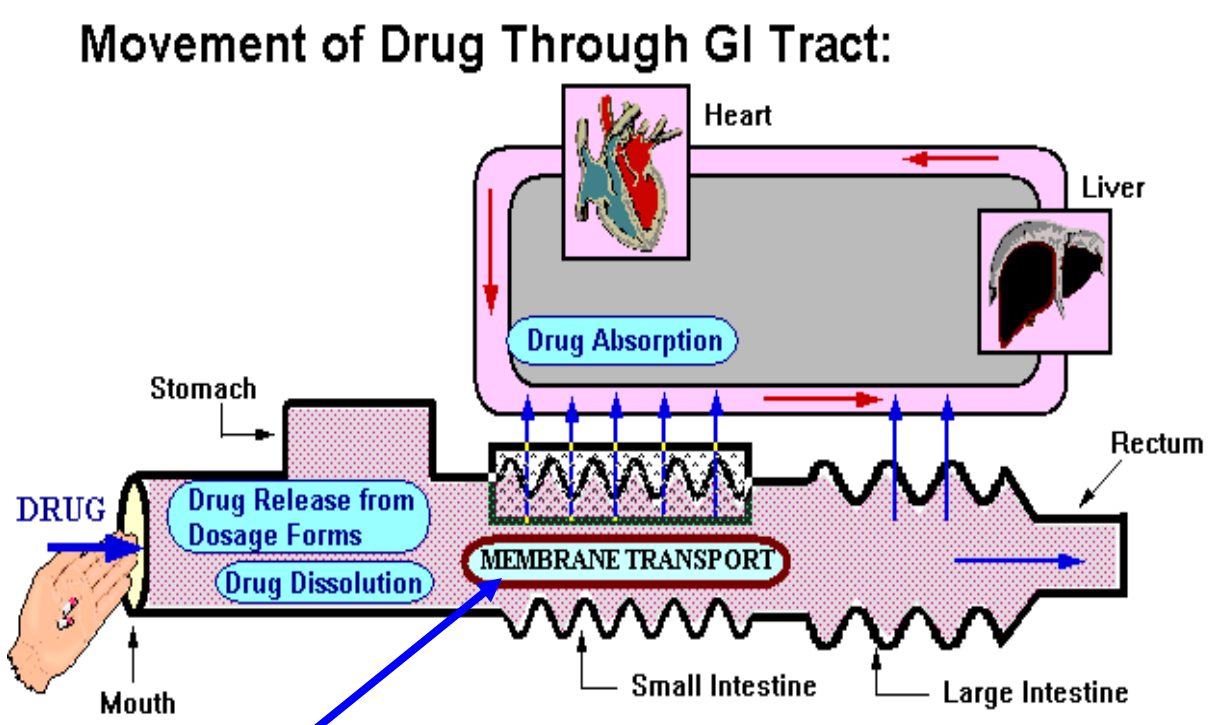
Absorption and BE: All Sites

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





Oral Products



$$\text{Flux} = j = P_{eff} \cdot C$$

Conflation of the Terms*

- Drug
- Drug Product

*this ambiguity reaches back as far as Section 6 of the Pure Food and Drug Act of 1906, which defines “drug” as “any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals,”

Fasted & Fed GI Motility Patterns

Fasted

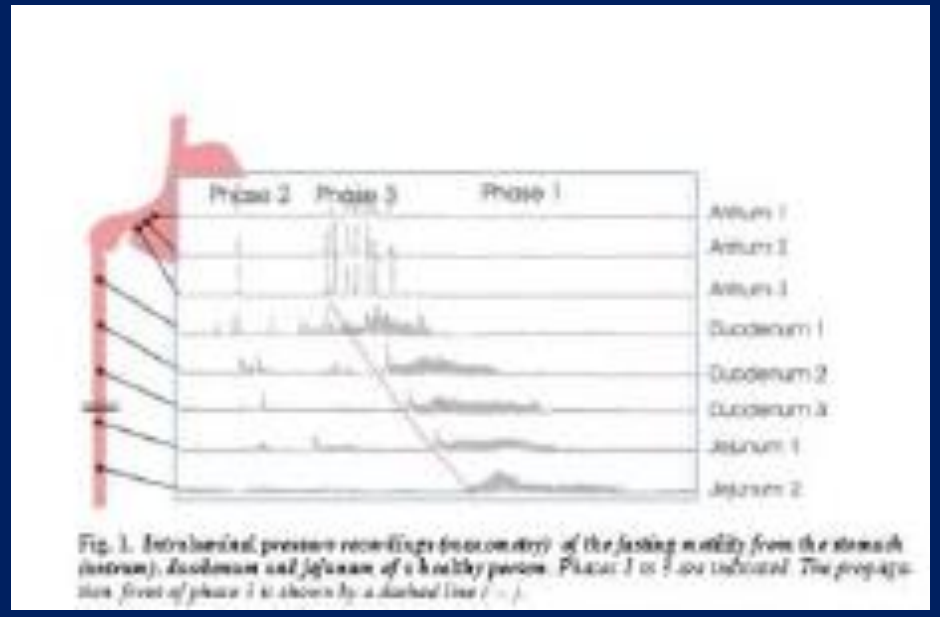


Fig. 1. *Intraluminal pressure recordings (manometry) of the fasting motility from the stomach (antrum), duodenum and jejunum of a healthy person. Phases 1 to 3 are indicated. The propagation front of phase 1 is shown by a dashed line (- - -).*

Fed

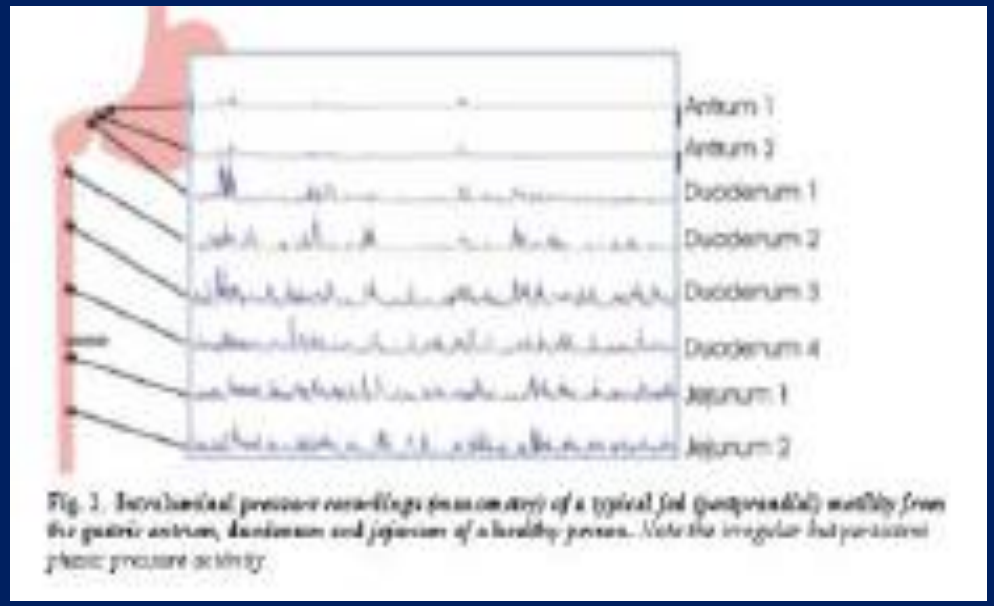


Fig. 2. *Intraluminal pressure recordings (manometry) of a typical fed (postprandial) motility from the gastric antrum, duodenum and jejunum of a healthy person. Note the irregular but persistent phasic pressure activity.*

Early Studies on Motility Phase Dependent Gastric Emptying & Intestnal Transit

Journal of Pharmacokinetics and Biopharmaceutics, Vol. 15, No. 5, 1987

PHARMACOMETRICS

The Influence of Variable Gastric Emptying and Intestinal Transit Rates on the Plasma Level Curve of Cimetidine; An Explanation for the Double Peak Phenomenon

Rebecca L. Oberle[1] and Gordon L. Amidon[1,2]

Received August 12, 1986—Final May 26, 1987

GASTROENTEROLOGY 1990;99:1275–1282

The Influence of the Interdigestive Migrating Myoelectric Complex on the Gastric Emptying of Liquids

REBECCA L. OBERLE, TZYY-SHOW CHEN, CHARLES LLOYD, JEFFREY L. BARNETT, CHUNG OWYANG, JAMES MEYER, and GORDON L. AMIDON

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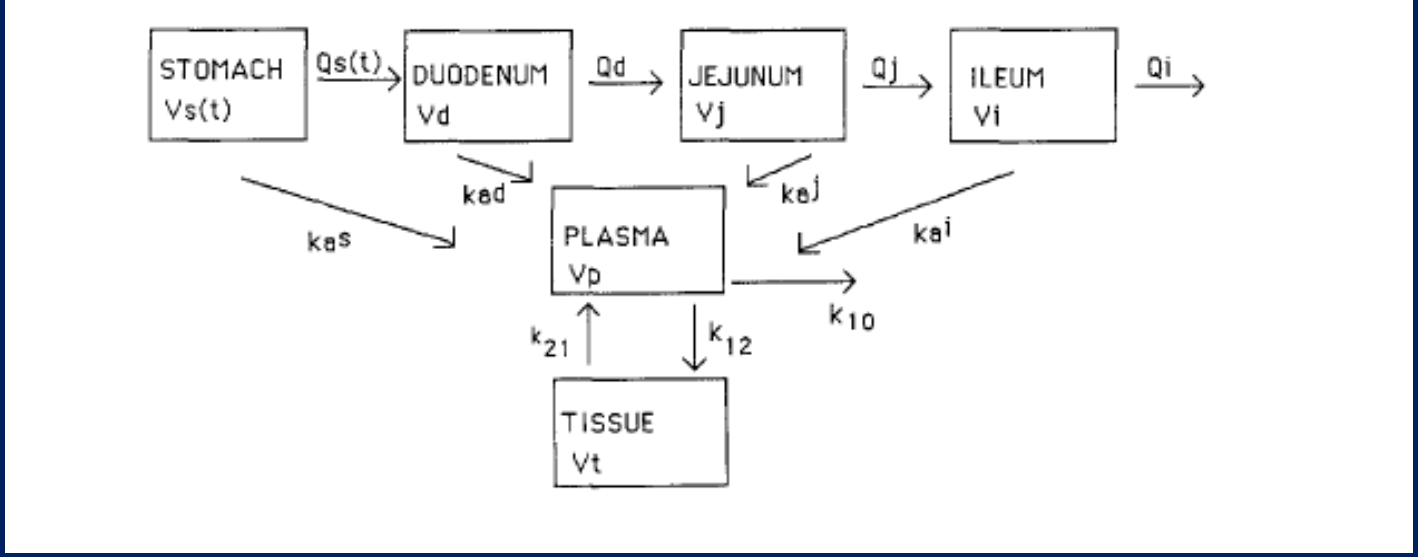
Early CAT Model (Cimetidine)*



* Oberle, cited

Motility & Phase Dependent Plasma Levels

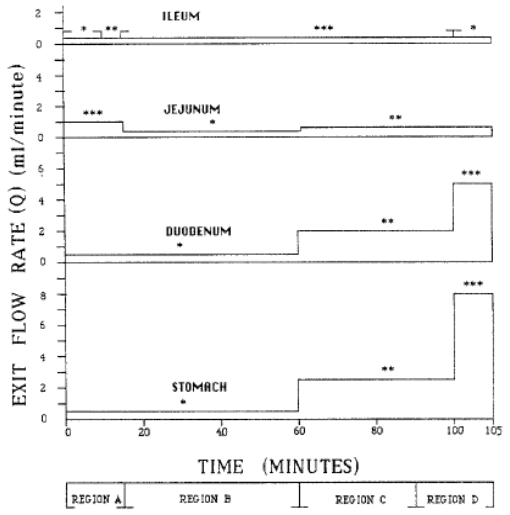


Fig. 2. Model flow rates as a function of gastrointestinal motility phase, depiction of the migrating myoelectric complex staggered down the GI tract, and illustration of defined regions A, B, C, and D (*-Phase I: **-Phase II: ***-Phase III).

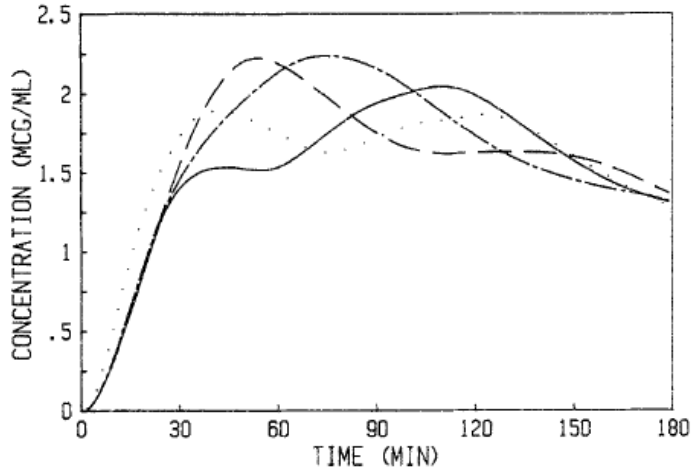


Fig. 3. Illustration of mean plasma concentration time profiles of cimetidine when drug is dosed in region A (——), region B (— - —), region C (- - -) and region D (. . . . .) (see Fig. 2).

Motility Dependent Gastric Emptying

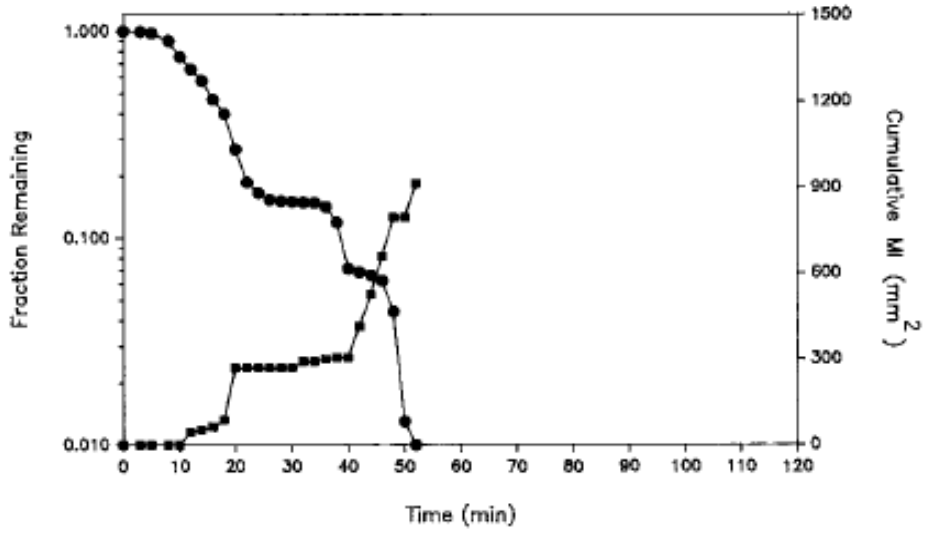


Figure 3. Sample gastric emptying curve showing deviations from log linearity. This pattern, showing a transient decrease in the gastric emptying rate, was found with approximately 10% of the 200-mL curves. In these cases, emptying correlated strongly with phasic activity. The plateau in emptying was associated with a period of quiescent motility.

Evolution of CAT Models 1990's

ELSEVIER

Advanced Drug Delivery Reviews 19 (1996) 359–376

advanced drug delivery reviews

Transport approaches to the biopharmaceutical design of oral drug delivery systems: prediction of intestinal absorption

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Abstract

For almost a half century scientists have striven to develop a theoretical model capable of predicting oral drug absorption in humans. From the pH-partition hypothesis to the compartmental absorption and transit (CAT) model, various qualitative/quantitative approaches have been proposed, revised and extended. In this review, these models are classified into three categories; quasi-equilibrium models, steady-state models and dynamic models. The quasi-equilibrium models include the pH-partition hypothesis and the absorption potential concept, the steady-state models include the film model and the mass balance approaches, and the dynamic models include the dispersion, mixing tank and CAT models. The quasi equilibrium models generally provide a basic guideline for understanding drug absorption trends. The steady-state models can be used to estimate the fraction of dose absorbed. The dynamic models predict both the fraction of dose absorbed and the rate of drug absorption and can be related to pharmacokinetic models to evaluate plasma concentration profiles.

Keywords: pH-partition hypothesis; absorption potential concept; mass balance approach; mixing tank; dispersion model; compartmental absorption and transit model

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International Journal of Pharmaceutics 186 (1999) 119–125

international journal of pharmaceutics

www.elsevier.com/locate/promis

A compartmental absorption and transit model for estimating oral drug absorption

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Abstract

This report describes a compartmental absorption and transit model to estimate the fraction of dose absorbed and the rate of drug absorption for passively transported drugs in immediate release products. The model considers simultaneous small intestinal transit flow and drug absorption. Both analytical and numerical methods were utilized to solve the model equations. It was found that the fraction of dose absorbed can be estimated by $F_a = 1 - (1 + 0.54 P_{eff})^{-7}$, where P_{eff} is the human effective permeability in cm/h. A good correlation was found between the fraction of dose absorbed and the effective permeability for ten drugs covering a wide range of absorption characteristics. The model was able to explain the oral plasma concentration profiles of atenolol.

Keywords: Drug absorption kinetics; Fraction of dose absorbed; Permeability; Compartmental modeling

Dispersion and CSTR Approaches*

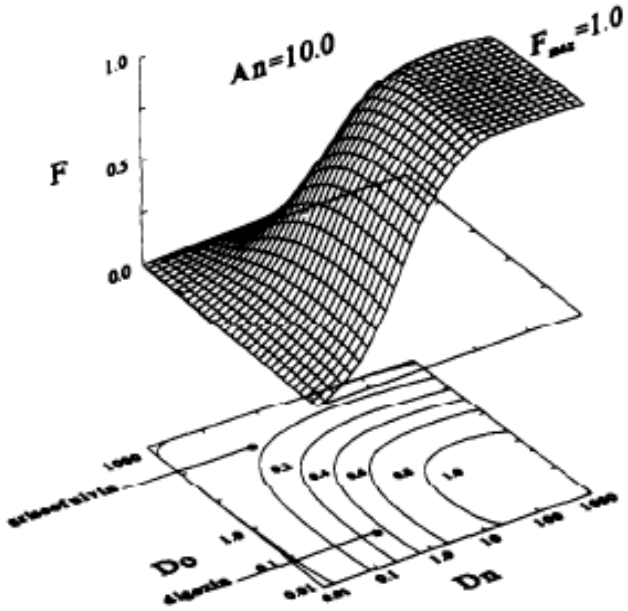


Fig. 1. Estimated fraction of dose absorbed vs dissolution number, *Dn*, and dose number, *Do*, for a high permeability drug. *An* = 10 corresponds to a drug with a permeability approximately that of glucose. *Dn* and *Do* for digoxin and griseofulvin were calculated from Eq. (26) and Eq. (2) and the following physicochemical/physiological parameters (from [5])

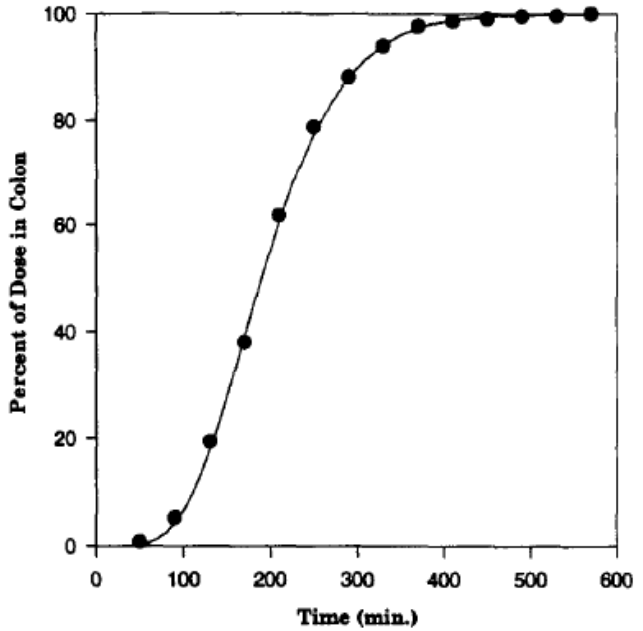
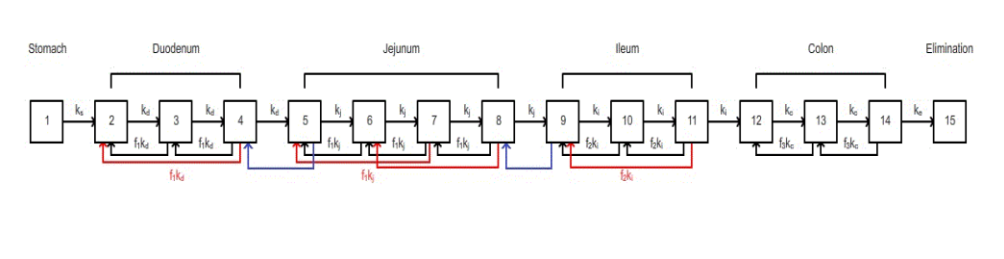


Fig. 4. Predicting human small intestinal transit flow by compartmental absorption and transit model, where (——) represents the compartmental absorption and transit model and (●) represents the cumulative percent of small intestine transit time.

*Yu, L. Et. Al. Adv. Drug Delivery, op. cit. (

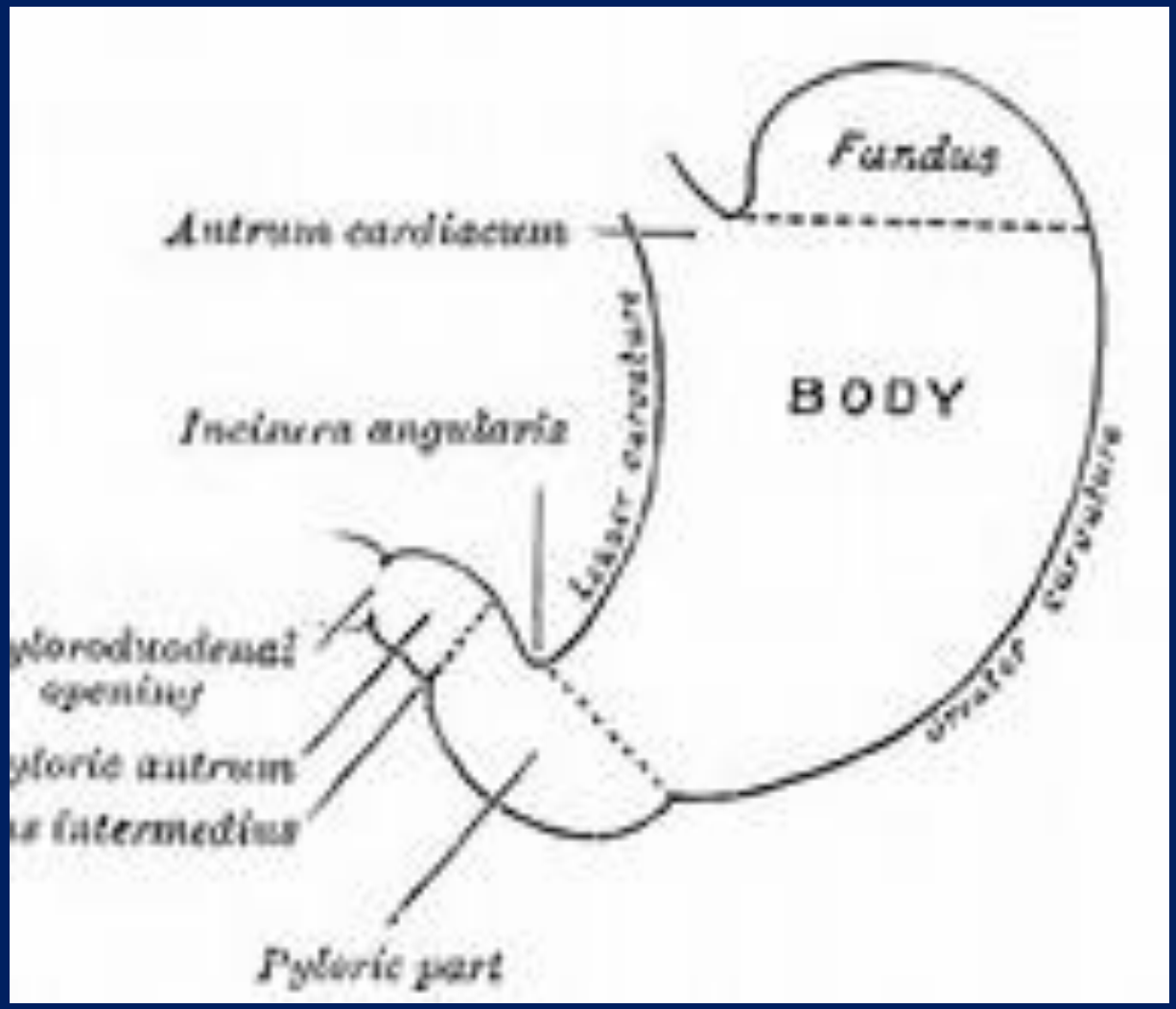
Elaboration of CAT Models



Intestinal Motility

- Fasted State
  - Segmental
  - Peristaltic
- Fed State

Stomach Functional Parts



Fasted State Gastric Emptying 1990 (200 ml)

GASTROENTEROLOGY 1990;99:1275–1282

The Influence of the Interdigestive Migrating Myoelectric Complex on the Gastric Emptying of Liquids

REBECCA L. OBERLE, TZYY-SHOW CHEN, CHARLES LLOYD, JEFFREY L. BARNETT, CHUNG OWYANG, JAMES MEYER, and GORDON L. AMIDON

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Fasted State Gsastric Emptying (Motility) Variation

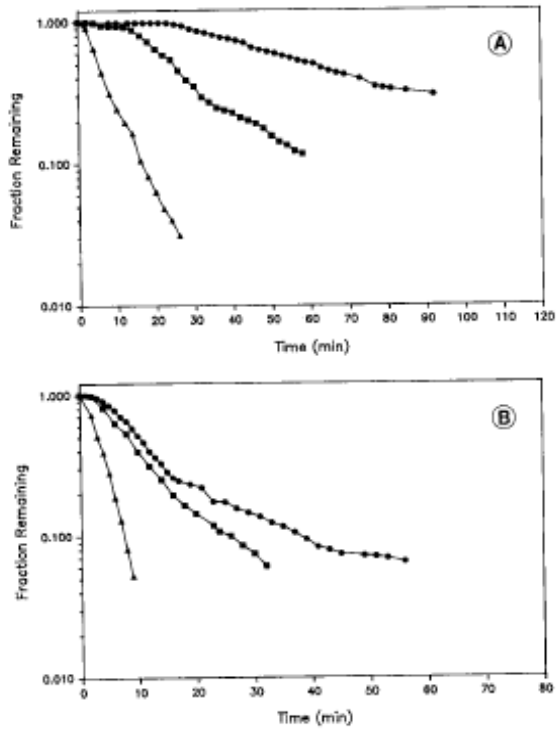
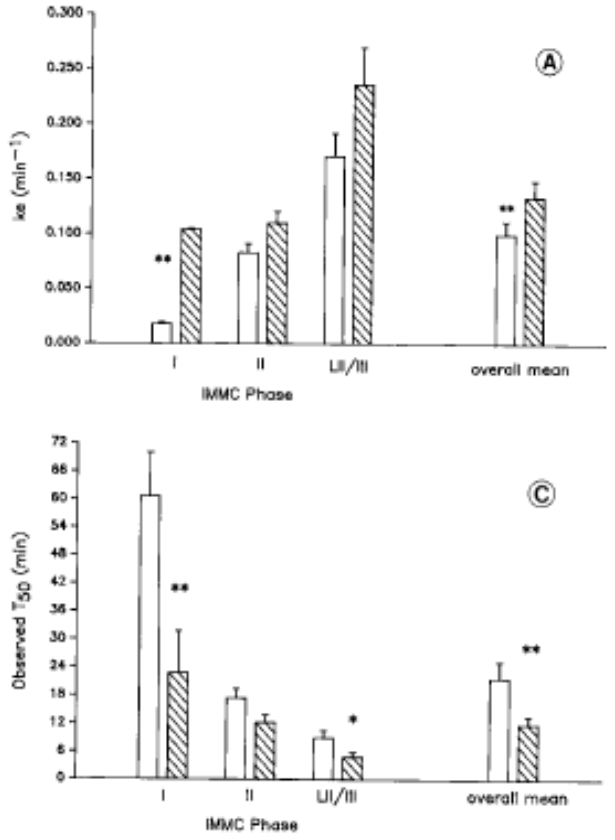


Figure 1. Gastric emptying patterns after administration of (*A*) 50 mL or (*B*) 200 mL during IMMC phase I (●), II (■), or III (▲). Gastric emptying of 50 mL was successively faster in phases I, II, and late II/III ($P < 0.05$). Gastric emptying rate of 200 mL in phase I was not significantly different from that in phase II. However, 200 mL emptied faster in late phase II/III than in phase I or II.



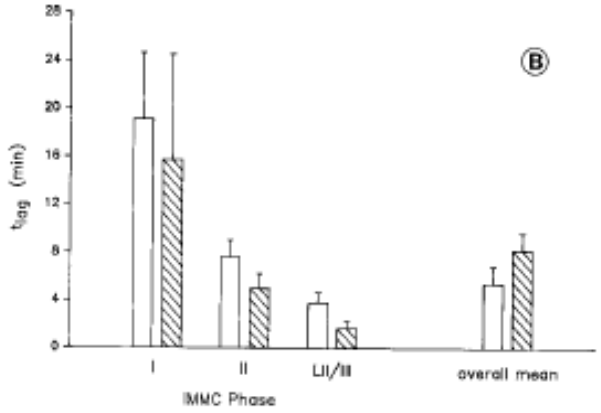


Figure 2. Comparison of (*A*) gastric emptying rate (k_e), (*B*) lag time (t_{lag}), and (*C*) observed T_{50} (T_{50}^{obs}) between 50- (open *bars*) and 200-mL (*striped bars*) volumes in IMMC phases I, II, and late II/III. Data expressed as mean ± SEM. $^*P < 0.05$. $^{**}P < 0.01$. There was a statistical difference in k_e and T_{50}^{obs} between 50- and 200-mL volumes during phase I and in T_{50}^{obs} in late phase II/III ($P < 0.05$). These results show that differences in gastric emptying rates will depend on volume in addition to existing IMMC phase. However, in general, 200 mL is expected to empty faster than 50 mL.

long, and 30% of the curves had lag times greater than

Fast Forward to 2016

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Article

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Gastrointestinal Motility Variation and Implications for Plasma Level Variation: Oral Drug Products

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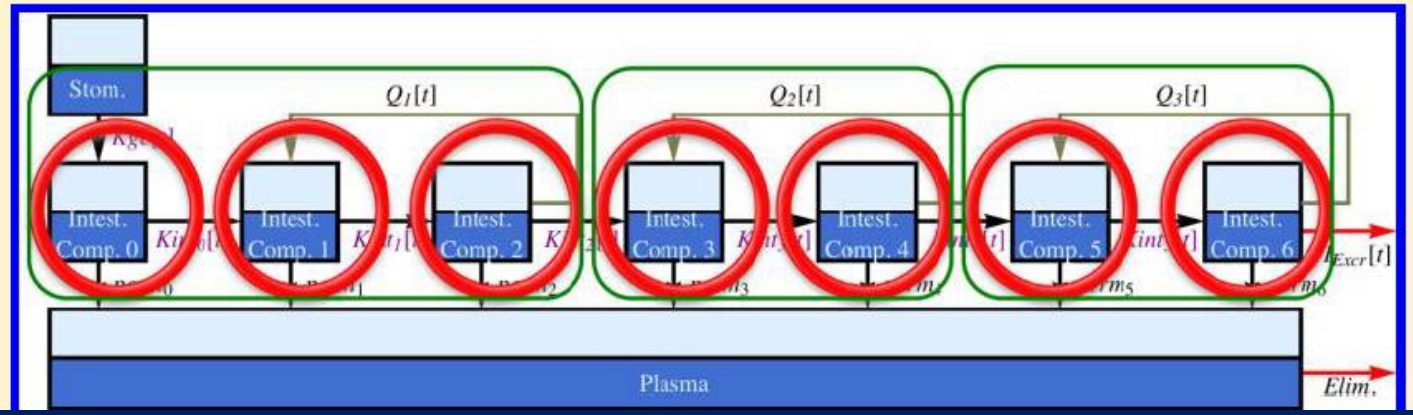


Dose Time (t_o)Relative to Fated State Phase

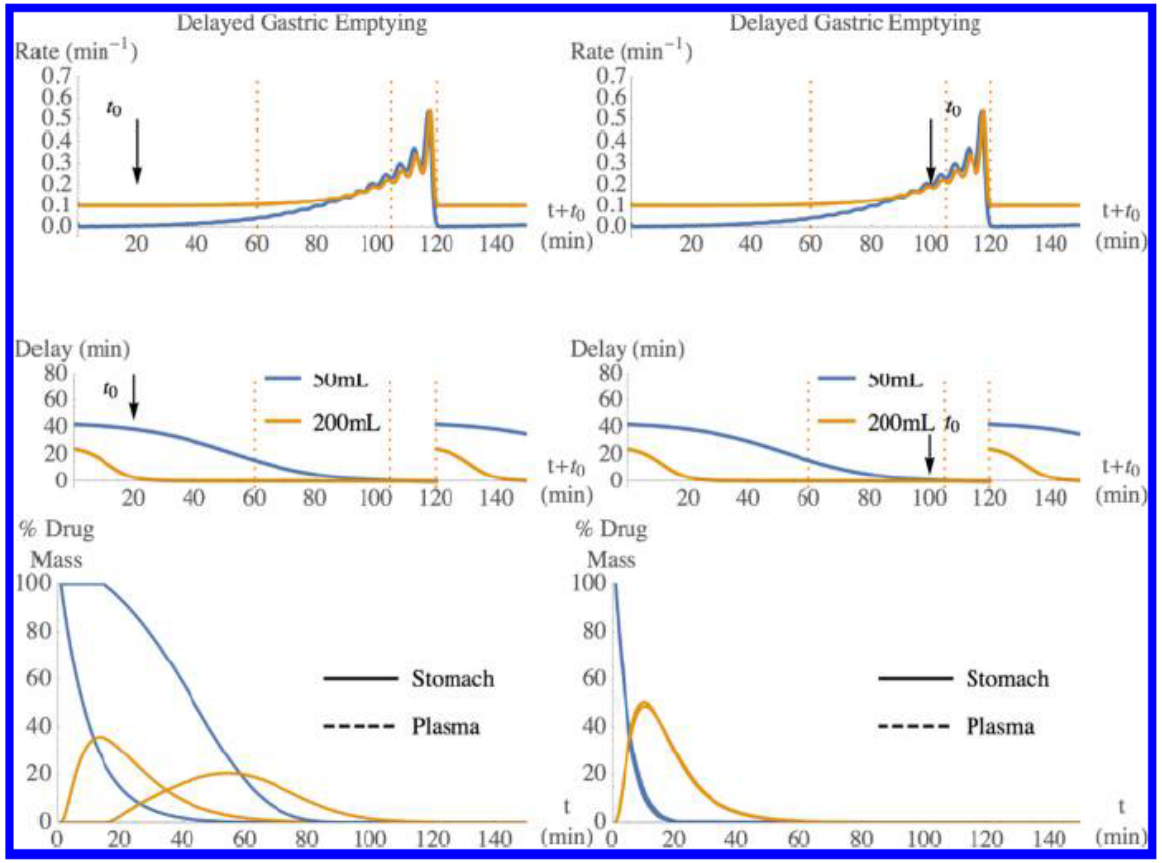


Figure 4. Effect of dose time t_0. Left: early dosing that corresponds to phase I with a low gastric emptying rate and long lag time; the volumetric lag time dependence results in a considerable difference in the emptying and appearance in plasma. Right: late dosing in phase III where the gastric emptying rate has increased considerably and the lag time is nearly zero; there is a negligible difference between the 50 and 200 mL volumes because all gastric content is emptying rapidly and immediately.

Simulated BE Trials: Gastric Emptying Variation in Plasma levels as a Function of to*

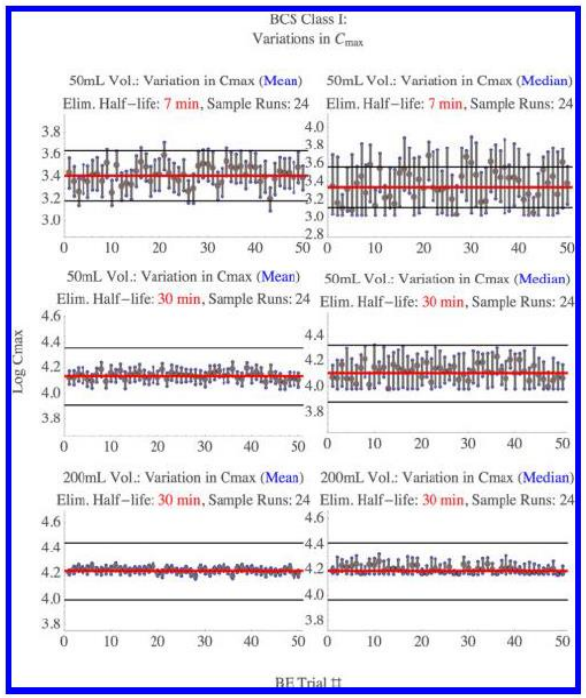


Figure 15. Simulated BCS Class I BE trials. The black horizontal bars represent the reference 80–125% range. The vertical bars are individual BE simulations with 24 virtual subjects each, indicating the C_{max} mean 90% CI. In the left column, the mean C_{max} is used, whereas the median is considered in the right column.

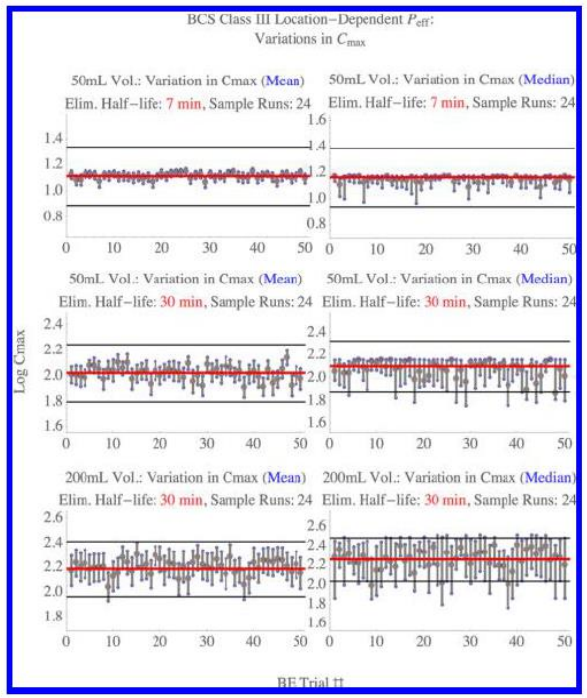


Figure 17. Simulated BCS Class III BE trials using location-dependent permeation. The vertical bars are individual BE simulations with 24 virtual subjects each, indicating the C_{max} mean 90% CI. In the left column, the mean C_{max} is used, whereas the median is considered in the right column.

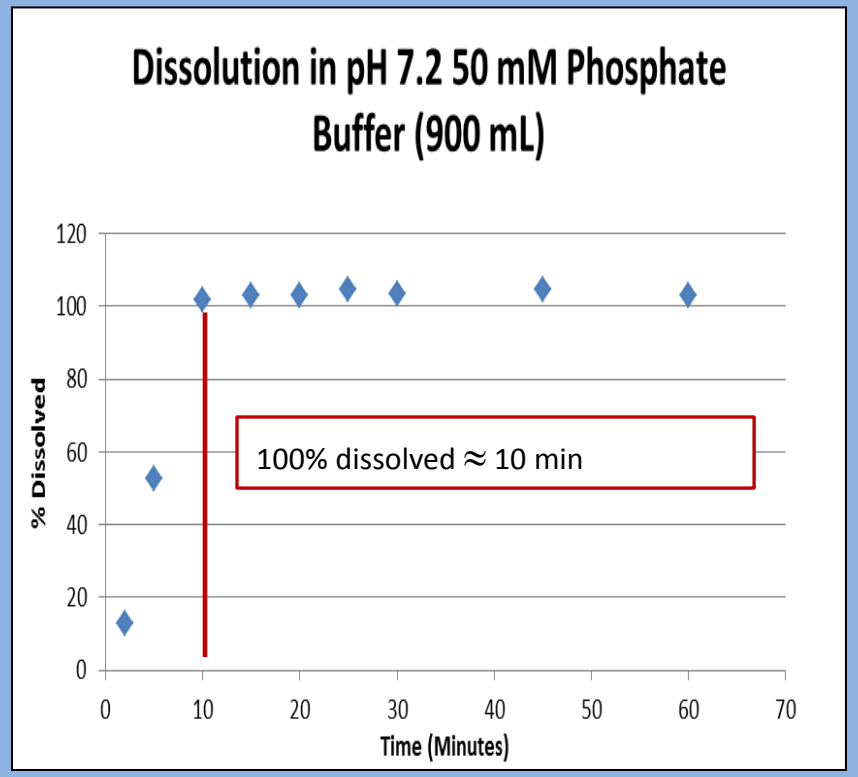
*to Dose relative to motility phase

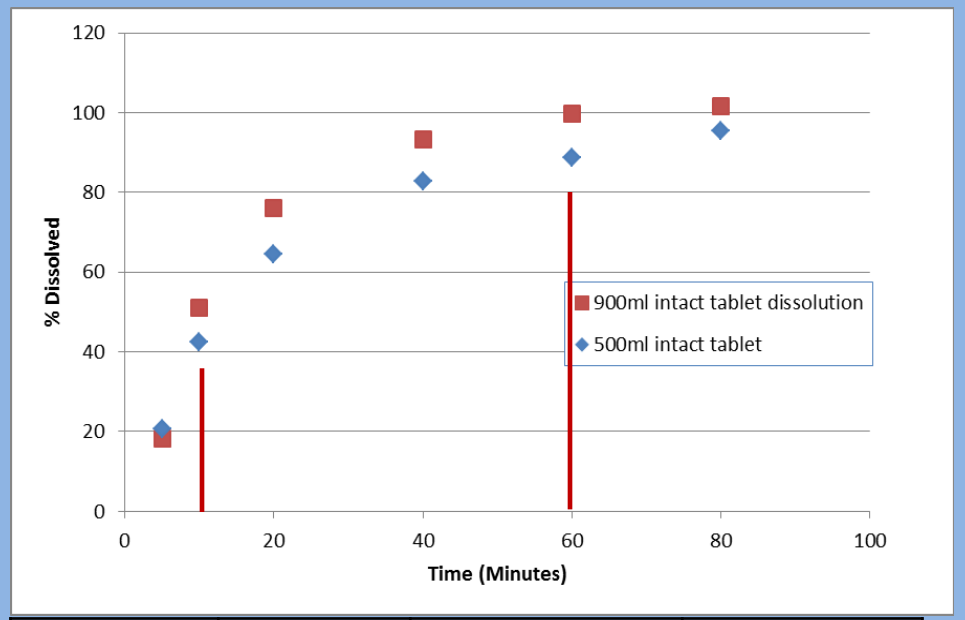
What about the GI Input?

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



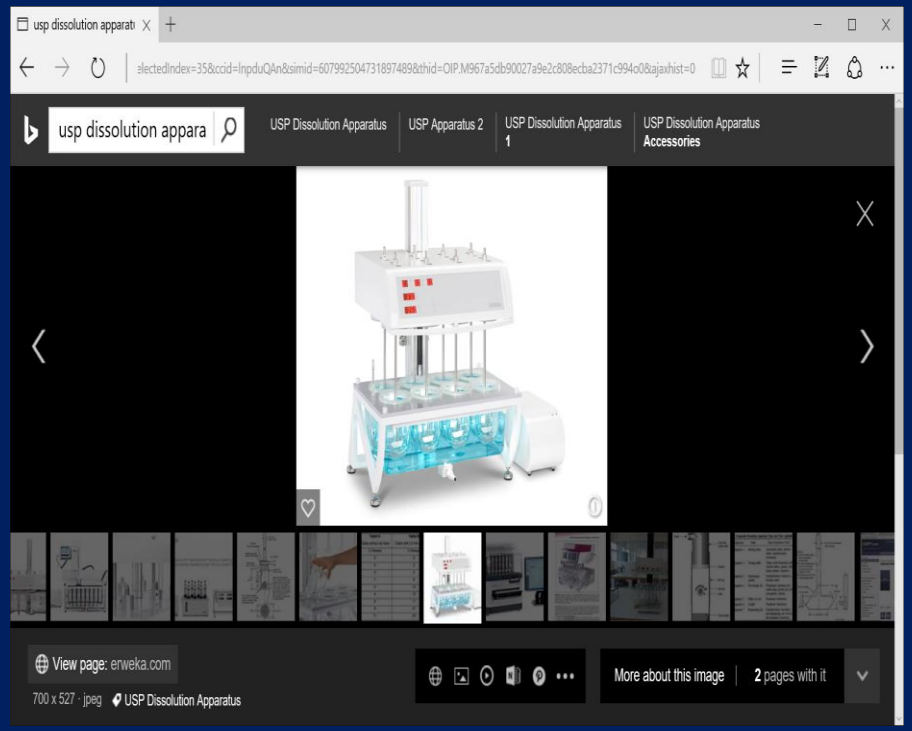


Bulk Volume, ml	Extent of dissolution	Time to dissolve 50% dose, min	Time to 100%, min
500	105%	13	80
900	102%	10	60

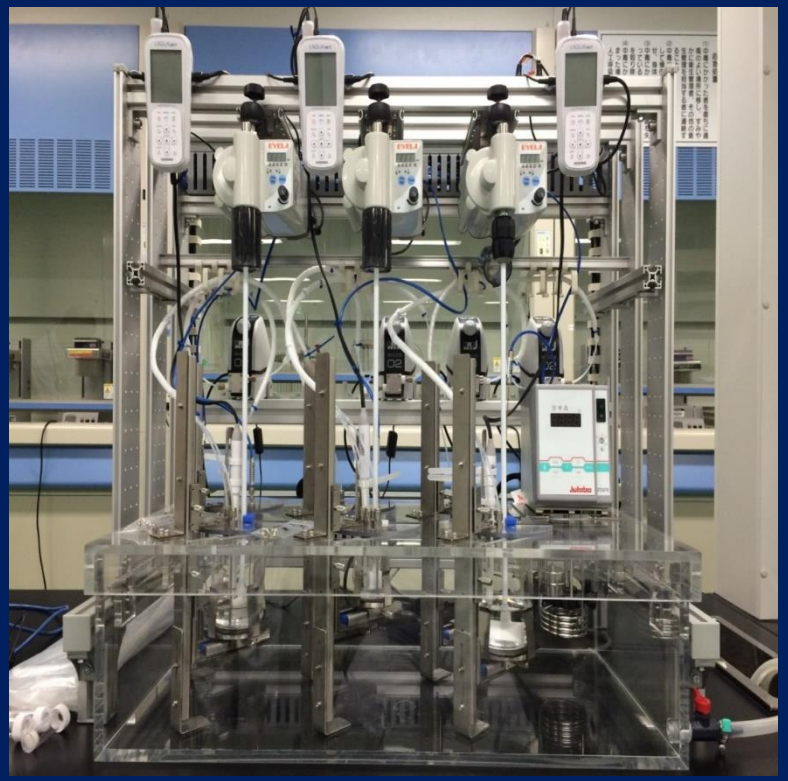
USP Test: pH =7.2 50mM Phoshate
50 RPM paddle (Apparatus 2)
Not Less Than 80% dissolved in 60 min

Transition to *in vivo* relevance

USP



iPD



Extending The Biowaivers via iPD?

- BCS Class I: Slower Dissolution?
- BCS Class III : Quantative same, Qualitative Similar
- BCS Class II & IV: SubClasses A,B, C

BCS Subclass: Absorption Profile

API

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

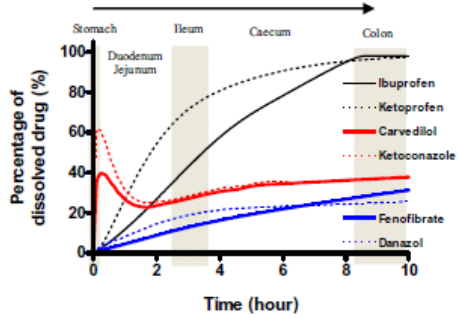


Fig. 2. Percentage of amount dissolved with an IR dosage. Black solid and dot lines represent BCS Class II weak acids, Red solid and dot lines represent BCS class weak bases and blue solid and dot lines represent BCS class neutrals. (For interpretation of the references to color in this figure legend,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

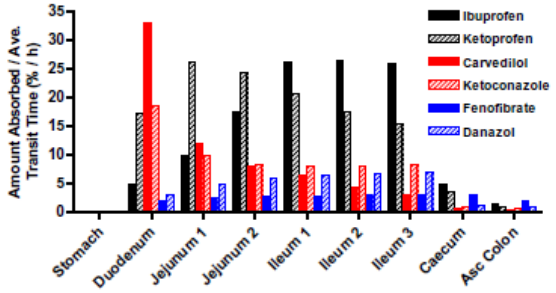


Fig. 3. The absorption rates of BCS Class II drugs in each GI segment. Percentages of amount absorbed after oral administration of an IR dosage are divided by the average transit time and are plotted as a function of each GI segment. Black bars represent BCS Class II weak acids, Red bars represent BCS 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)

Gordon's real BCS

solubility

hi → lo

permeability

lo → hi

formulation ← Purgatory ↑

bioavaila-bility limbo →