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

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Absorption and BE: All Sites

\[ M_{abs}(t) = \int_{0}^{t} \int_{A} (P_{eff} \cdot C) dA dt \]
Oral Products

Movement of Drug Through GI Tract:

Flux = \text{Flux} = \text{eff} \cdot P \cdot C

 Flux = j = P_{\text{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

Fed
Early Studies on Motility Phase Dependent Gastric Emptying & Intestinal 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. Oberle¹ and Gordon L. Amidon¹,²
Received August 12, 1986—Final May 26, 1987

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

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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 1, **Phase 2, ***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

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, refined 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 approach, and the dynamic models include the dispersion, mixing tank and CAT models. These 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

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 \( F_a = 1 - \left(1 - 0.54 \cdot P_{ma}\right)^{-1} \), where \( P_{ma} \) 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. © 1999 Elsevier Science B.V. All rights reserved.

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, $D_m$ and dose number, $D_o$, for a high permeability drug. $A_n-10$ corresponds to a drug with a permeability approximately that of glucose. $D_m$ and $D_o$ 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.

Elaboration of CAT Models

Intestinal Motility

• Fasted State
  – Segmental
  – Peristaltic
• Fed State
Stomach Functional Parts
The Influence of the Interdigestive Migrating Myoelectric Complex on the Gastric Emptying of Liquids

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Fasted State Gastric Emptying (Motility) Variation

Figure 1. Gastric emptying patterns after administration of (A) 50 ml or (B) 200 ml during IMMC phase I (I), II (II), or III (III). Gastric emptying of 50 ml was successively faster in phases I, II, and late 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 for II.

Figure 2. Comparison of (A) gastric emptying rate (k), (B) lag time (t_L), and (C) observed T_50 (I) vs. T_50 (II, III) between 50-ml (open bars) and 200-ml (striped bars) volumes in IMMC phases I, II, and late III. Data expressed as mean ± SEM. *P < 0.05, **P < 0.01. There was a statistical difference in k, and T_50 between 50- and 200-ml volumes during phase I and in T_50 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.
Fast Forward to 2016
Dose Time ($t_o$) Relative to Fated State Phase

Figure 4. Effect of dose time $t_o$. 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*

*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))

800 mg intact tablet dissolution in pH 6.5, 10 mM HCO₃ buffer (15% CO₂ & total buffer concentration of 14 mM). USP 2 apparatus, 50 rpm & 37 °C

<table>
<thead>
<tr>
<th>Bulk Volume, ml</th>
<th>Extent of dissolution</th>
<th>Time to dissolve 50% dose, min</th>
<th>Time to 100%, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>105%</td>
<td>13</td>
<td>80</td>
</tr>
<tr>
<td>900</td>
<td>102%</td>
<td>10</td>
<td>60</td>
</tr>
</tbody>
</table>

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

100% dissolved ≈ 10 min
Transition to *in vivo* relevance

USP

iPD
Extending The Biowaivers via iPd?

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

API

• A= Acid
• B=Base
• C=Neutral
# BCS SubClasses

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>0.1 N HCl</th>
<th>pH 6.5</th>
<th>Permeability</th>
<th>Media*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>PIB**</td>
</tr>
<tr>
<td>IIa</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>15 and 30 min in PGB**, then PIB**</td>
</tr>
<tr>
<td>IIb***</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>15 or 30 min in PGB**, then PIB**</td>
</tr>
<tr>
<td>IIc</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Dissolution 15 and 30 min in PGB**, Then PIB** + surfactant to match in vivo solubilization</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Same as I</td>
</tr>
<tr>
<td>IVa</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Same as IIa</td>
</tr>
<tr>
<td>IVb**</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Same as IIb**</td>
</tr>
<tr>
<td>IVc</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Same as IIc</td>
</tr>
</tbody>
</table>
A Key to Prediction is the Input $I(t)$, Concentration of Drug at the Absorbing Site(s)