Biophysical Modeling of Gastrointestinal Drug Absorption: Challenges & Innovation

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Abstract
Biophysical modeling of gastrointestinal (GI) drug absorption is a critical aspect improving oral drug delivery and supporting personalized medicine [1]. This paper discusses recent developments of biologically-accurate pharmacokinetic (PBPK) modeling, particularly through the integration of convection-diffusion
equations, permeability-limited absorption models, and stochastic transit models [6]. Some studies have also employed computational fluid dynamics (CFD) and microbiome modeling, involving sources of physiological variability (e.g., pH, motility and gut bacteria) [7]. Provided collectively, the literature listed the following parameters that need to be identified: permeability, intestinal area, motility, degradation, and diffusion coefficient. Common validation methods identified in prior studies were: in vitro assays (Caco-2 and gut-on-a-chip) and sensitivity analysis. Overall, based on this review, the modelling techniques described in literature can offer increased accuracy in predicting GI absorption, when measured with complex drugs, that lend themselves to future development of personalized oral therapies.

Keywords: Gastrointestinal Drug Absorption; PBPK Modeling; Convection-Diffusion Equation; Permeability-Limited Absorption; Personalized Oral Drug Delivery.

Introduction

Background, Biophysical Implication, Scientific Impact, Innovation

The absorption of drugs in the GI tract is arguably the most important factor in determining treatment outcome for drugs given by oral route. For a drug to enter systemic circulation it must survive an acidic gastric environment, dissolve in intestinal lumen fluids, then permeate the epithelial lining of the intestines. These steps are influenced by local physiological factors such as pH, intestinal motility, enzymatic degradation and membrane permeability [1, 2]. From a biophysical view, GI absorption is driven by physical transport mechanisms - diffusion, convection, enzymatic hydrolysis, and membrane-mediated uptake. These mechanisms combined with the local physiology, describe the absorption characteristics of a given compound [6, 12]. Physiologically based pharmacokinetic (PBPK) models combine all of these physiological processes into system-level simulations of luminal transport and epithelial permeation [6]. PBPK modeling advances a mechanistic understanding of the inter-individual variability that drives differences in drug uptake and provides improved predictions of bioavailability across a population of patients [5, 9]. These models support rational design processes and optimization of dosing by giving unique insight into variation in compartments along the gross anatomy GI tract, where parameterization describes a specific physiology. This paper presents a new modeling platform that builds on recent innovations in computational fluid dynamics (CFD), stochastic transit models, and microbiome-based absorption kinetics. These advancements improve the spatio-temporal resolution and applicability of personalizing drug delivery applications [7, 8].

Literature Review, Research Gaps, Motivation and objectives

The absorption of gastrointestinal (GI) drugs is a multi-scale physiological process, critical to the bioavailability of orally delivered therapeutics delivered [1, 3]. Once a drug is ingested, it must tolerate the acidic environment of the stomach, dissolve into the fluids of the intestines, and pass through the epithelial lining in order to enter circulation. The efficiency of uptake is dictated by region-specific factors, including pH, motility, enzymes, and membrane permeability [5,9]. Biophysical modeling takes such factors and creates quantitative representations governed by physical laws (e.g., diffusion, convection, membrane-limited transport) to enable a spatio-temporal modeling of the behaviors of drugs traversing through the GI tract [6, 15].Early approaches, including the pH-partition hypothesis, were able to make only very coarse estimates towards absorption via compartmental models. The development of PBPK modeling simulation of drug uptake linked additional features such as gastric emptying, degradation by enzymes, and first-pass metabolism

in the liver through mathematical representations [3,6,9]. Recent work has focused on spatially distributed models and machine learning methods that could predict the distribution and absorption patterns of drugs in each distributional region from clinical and in-vitro data [7, 8].When it comes to the advances in oral GI absorption modeling, there are still limitations. Most models still present overly simplistic assumptions of regional physiological variation such as pH, intestinal blood flow, and motility, as well as omission of interactions due to food intake, and understanding the role of the gut microbiome [9, 11]. Current modeling frameworks also often lack mechanistic detail sufficient to enable simulations of the drug modalities that are included in the more complex chemical classes in the pharmaceutical industry such as peptides and nanoparticles. Current approaches that rely on machine learning provide predictive ability but often require large datasets that provide little understanding of the physiological mechanisms involved [7]. To address the limitations, in this paper we will summarize some of the recent advances from previous work to modify PBPK models in order to integrate: (i) regional physiological factors such as pH, permeability, motility, and intestinal blood flow [6]; (ii) food effects and more advanced drug classes [10]; and (iii) model validation involving Caco-2 assays, gut-on-a-chip platform experimentation, and computational sensitivity analysis [8].Our motivation in this work is to combine and summarize these advances to improve the physiological plausibility and predictive modeling of GI absorption. The focus will lead to subsequent discussions about the potential to develop and tailor approaches for personalized oral drug delivery approaches.

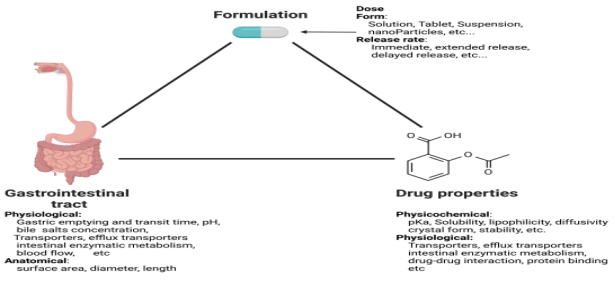

Figure 1: *Key factors influencing gastrointestinal drug absorption, including physiological and anatomical features of the GI tract, physicochemical and biological properties of the drug, and formulation parameters that determine dose form and release characteristics [7].*

Methods - Overview

This research utilizes an integrated biophysical modeling approach to simulate GI absorption of drugs, incorporating PBPK models, CFD modeling, and microbiome-interaction modeling to achieve both mechanistic richness and physiological realism.

Cross-sectional PBPK models represent the GI tract as an assemblage of compartmentalized regions and employ physiological variables e.g., pH, GI motility, enzymatic processes, permeability, and blood flow capacity to simulate the eventual phases of drug dissolution, luminal transport and systemic absorption [6, 9]. CFD extends the PBPK framework, allowing for convective and diffusive solute transport in the intestinal fluids, facilitating simultaneous resolution of spatial-temporal concentration gradients in different compartments [12]. Microbiome-integrated modeling considers microbial metabolism, an important source of inter-individual variability of oral bioavailability, expanding the model's ability to account for patient-specific absorption processes [8].

Collectively, this suite of modeling strategies enables system-wide pharmacokinetic predictions, localized drug absorption profiling and patient-specific variability assessments, and ultimately guides the development of more predictive and personalized drug delivery strategies. It is the combination of these two complementary modeling approaches that set this biophysical modeling framework apart from traditional, single-layer models, addressing limitations in mechanistic fidelity and translational relevance.

Model validation is performed via both experimental and computational methods. Experimental validation consists of Caco-2 cell permeability assays, gut-on-a-chip microphysiological systems, and in vivo animal studies that reproduce dynamic intestinal conditions and define benchmarks for absorption behavior [3,10]. Computational validation consists of global sensitivity analysis and parameter optimization approaches that characterize the impact of relevant physiological parameters on model outputs [7]. Validation ultimately supports model robustness, reproducibility, and applicability of the model to clinical and formulation real-world scenarios.

Methods - Governing Equations and Parameterization

The study incorporates three fundamental governing equations into PBPK modeling framework to enable mechanistic simulation of GI drug absorption. Each governing equation is solved according to analytic or numerical applications based on both structural and physiological complexity. The parameters were obtained from or calculated from published validated experimental data and were optimized to some degree using a sensitivity analysis of the model outputs including concentration profiles, absorption rates, and transit profile data. **The first equation** governs the spatial and temporal evolution of drug concentration in the intestinal lumen, modeled using the convection –diffusion –degradation equation:

$$\frac{\partial C}{\partial t} + v\frac{\partial C}{\partial x} = D\frac{\partial^2 C}{\partial x^2} - k_{deg}C$$

Here, $C(x,t)$ represents the drug concentration as a function of position and time, v is the luminal flow velocity (cm/s), D is the diffusion coefficient (cm²/s), and k_{deg} is the first-order degradation rate constant (1/s), capturing enzymatic and microbial breakdown. This partial differential equation is solved numerically using a finite difference scheme with backward Euler time-stepping and central differencing in space to maintain stability under physiological flow conditions. Initial conditions assume a bolus dose, $C(x,0) = C0$, while boundary conditions are set as either no-flux ($\partial C / \partial x = 0$) or absorptive at the intestinal ends. The model output is a concentration profile over time and space, which determines local drug availability for absorption. The parameters v, D, and k_{deg} control how rapidly the drug moves, disperses, and degrades in the lumen.

The second governing equation models the rate of drug transport across the intestinal epithelium based on concentration gradients, expressed as:

$$R = P_{eff} \times A \times (C_{lumen} - C_{blood})$$

In this equation, R is the absorption rate (mg/min), P_{eff} is the effective permeability coefficient (cm/min), A is the absorptive surface area (cm²), C_{lumen} is the luminal concentration, and C_{blood} is the concentration at the basolateral (blood) side. This equation enables bidirectional flux and is numerically implemented as a flux boundary condition coupled to the convection diffusion solver. It is evaluated dynamically at each time step to reflect changes in concentration during drug transit. The output is a time-resolved absorption rate contributing to systemic bioavailability. The key parameters P_{eff}, A, and the luminal to blood gradient govern the rate and directionality of epithelial drug uptake.

The third governing equation models the progression of the drug through successive intestinal segments using a first-order compartmental transit model:

$$\frac{dM_i}{dt} = k_{tr}(M_{i-1} - M_i)$$

Here, $M_i(t)$ denotes the drug amount in compartment i (e.g., duodenum, jejunum), M_{i-1} is the amount in the preceding segment, and k_{tr} is the transit rate constant (1/min), which reflects physiological motility. This set of coupled ordinary differential equations is solved numerically using time-stepping algorithms (e.g., Euler or Runge-Kutta methods). Initial conditions specify that the dose is localized in the first compartment ($M_0 = \text{Mdose}$, $M_i = 0$ for $i > 0$). The output is the time-dependent drug amount in each region, which informs local exposure and absorption potential. The parameter k_{tr} controls the duration of residence in each segment, thereby influencing regional absorption windows.

Together, these three equations form an integrated system that resolves the full dynamics of oral drug absorption from dissolution and degradation, to transport across the intestinal wall, to spatial distribution along the GI tract. The six essential physiological parameters flow velocity (v), diffusion coefficient (D), degradation constant (k_{deg}), effective permeability (P_{eff}), surface area (A), and transit rate (k_{tr}) each play a distinct role in shaping the model's predictive outputs. These parameters were selected based on established literature and adjusted during model calibration to simulate drug behavior under realistic physiological conditions [6,7,9].

As shown in **Figure 2**, the modeling framework is summarized in a flowchart outlining five core

components: governing equations, numerical solution methods, boundary and initial conditions, validation strategies, and model outputs. The governing equations are solved using MATLAB's ODE solvers for ordinary differential equations and finite difference methods for partial differential equations. The resulting drug concentration and absorption profiles will be presented in the *Results* section. The flowchart also highlights the model validation process, which is supported by experimental studies such as gut-on-a-chip assays and sensitivity analyses to evaluate reliability. This structured framework supports applications in simulating systemic drug uptake across individuals and can be extended to patient-specific or disease-based modeling.

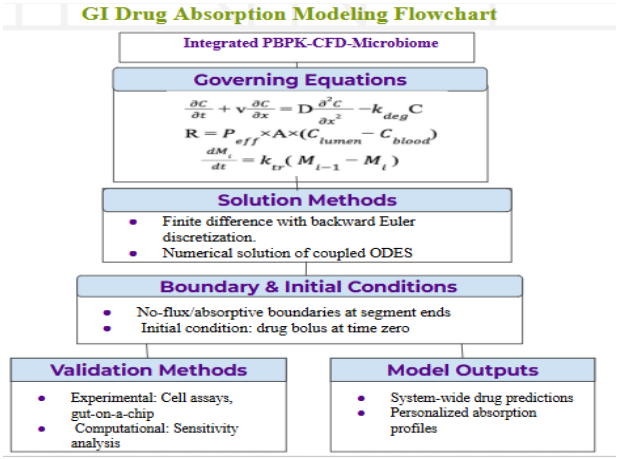

Figure 2. *GI drug absorption modeling framework showing governing equations, solution methods, boundary and initial conditions, validation strategies, and model outputs.*

Results and Discussion

Since the convection–diffusion–degradation governing equation includes two inputs, its output was expressed as a meshgrid plotted in MATLAB over time and space, as shown in **Figure 3** below. The parameters of v, D, and k_{deg} were set to 1 cm/s, 0.1 cm²/s, and 0.05 s^{-1}, respectively, as arbitrary values that vary among different drugs and physiology, but nevertheless reflect real-world conditions. The peak in drug concentration C(x,0) indicated the location where the drug is initially concentrated in the bolus dose. Over time, this peak became smaller, showing the effects of drug diffusion out of the bolus, followed by eventual degradation. The peak also shifted its position further along the intestinal lumen as time went on, due to the influence of its flow velocity (v) through the GI tract, which in turn was impacted by gut motility and the presence of food.

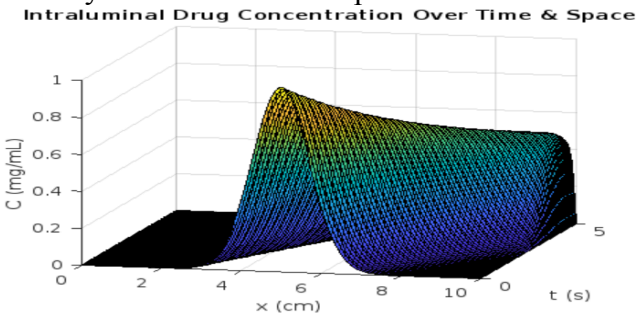

Figure 3. *Plot of* ***Intraluminal Drug Transport and Degradation****, showing drug concentration C over space x and time t with v = 1 cm/s, D = 0.1 cm²/s, and kdeg = 0.05 s^{-1}.*

Computational sensitivity analysis showed that at a given point in time, altering v and k_{deg} had stronger effects on the spatial distribution of drug concentration than D did, so in this particular context, altering the drug's diffusivity would not significantly change how it is processed by the body. As expected, increasing degradation rate constant k_{deg} caused drug concentration C to decline more steeply with increasing distance from its peak, while higher values of v had the opposite effect, in which greater amounts of drug spread out over a longer distance. Improving drug stability - including under low pH conditions in the stomach - and administering doses in coordination with food intake would therefore favor a more even distribution of drug in the small intestine.

Figure 4 displays the output of plotting trans-epithelial drug absorption rate R versus C_{blood} with varying values of effective permeability coefficient P_{eff}. Surface area A was set equal 300000 cm², based on the average adult small intestine, while P_{eff}'s value of 0.0003 cm/min was taken from experimental Caco-2 data in other sensitivity analyses [23, 24]. With R as the range of change in C_{blood} over time, driven by differences in drug concentration between the intestinal lumen and blood, R decreased with rising C_{blood} as more drug got absorbed into systemic circulation. Increasing P_{eff} and A both had the effects of increasing initial rates of absorption while also causing R to approach zero faster, given the greater permeability and

available surface area. On the other hand, increasing C_{lumen} while keeping other parameters constant resulted in higher initial R values without changing their rates of decline, so higher luminal drug concentrations produced higher blood drug concentrations within similar timeframes to lower initial C_{lumen} values.

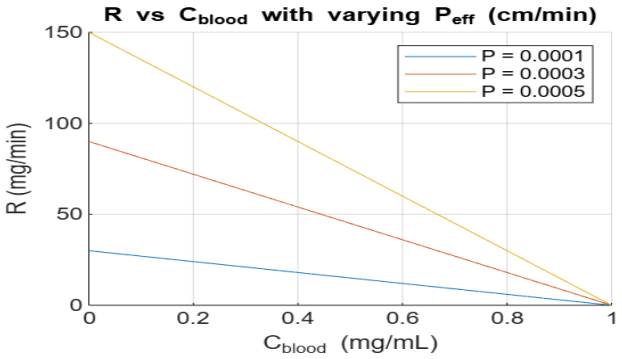

Figure 4. *Plot of* ***Trans-Epithelial Drug Absorption****, showing absorption rate R versus Cblood for varying Peff, with A = 300000 cm² and Clumen = 1 mg/mL.*

For the last governing equation, mass of drug M_i in compartment i - starting from an initial value of 1 mg - is plotted over time t for various transit rate constants k_{tr} in **Figure 5**, showing that M_i decreases over time, with the rate of change in drug mass eventually reaching zero. Higher k_{tr} values, as expected, increased the initial rate of M_i decline so that the drug left compartment i more quickly. In subsequent compartments, M_i increased as the drug began to enter them, with a similar declining rate of change, until mass was evenly distributed amongst compartments for more efficient absorption.

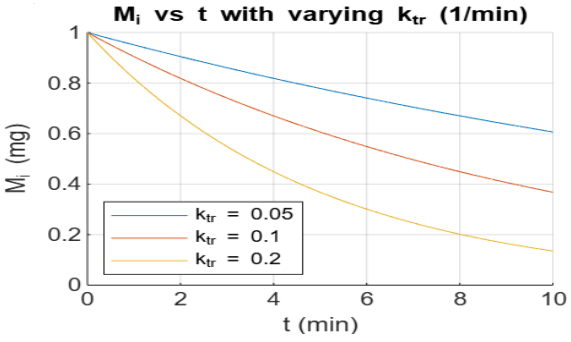

Figure 5. *Plot of* ***Segmental Transit Through GI Tract****, showing mass of drug Mi in segment/compartment i over time with varying ktr.*

Experimental validation was performed for midazolam metabolism by the cytochrome P450 enzyme CYP3A4 using the Fluid3D-X microphysiological system as a gut-on-a chip [10]. This system improved the accuracy of enzymatic expression from prior Caco-2 assays to reflect in vivo expression across different intestinal segments more accurately. Adding metabolic inhibitors was shown to increase net midazolam transport from the apical to basal sides of the device, since less drug was being metabolized within the gut. This was contrasted with other drugs such as quinidine and sulfasalazine, which favored basal-to apical transport. These experiments demonstrated the efficacy of assessing the role of GI-associated enzymatic expression and activity in drug metabolism. Data on GI tract permeability to drugs was successfully validated for passive transport via Caco-2 cell assays [9]. Additional modeling of pH effects on drug metabolism, based on the Henderson–Hasselbach equation, showed strong agreement with experimental data on peripheral blood concentrations of various drugs over time [6]. In conjunction with the governing equation for trans-epithelial absorption, these validation techniques could predict how much drug ultimately ends up in systemic circulation for bioavailability to targets beyond the GI tract.

Conclusion

Computational validation of drug metabolic patterns with three governing equations showed how a myriad of factors can have multi-faceted effects on how drugs undergo transport and diffusion through the GI tract, and how much is absorbed versus degraded over time. Experimental validation was useful for considering the impact of other factors, such as enzymatic activity and pH, in order to maximize the physiological accuracy of existing models.

The potential medical and research applications for these findings include making better predictions of drug efficacy from patients' physiological traits to optimize personalized medicine, or elucidating properties like diffusivity and permeability of novel drugs from clinical trial data. Expansion of validation methods to in vivo models in animals and, eventually, human patients will be an essential aspect of future research endeavors in this area.

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