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Combined PBM-PBPK Modeling for Optimized Integrated Oral Solid Dosage Form and Dosing Strategy Design

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ABSTRACT

The formulation of oral solid dosage forms can have a significant impact on drug bioavailability, particularly for poorly soluble drugs. However, traditional formulation development relies heavily on extensive experimental testing, which limits its efficiency and effectiveness in oral drug product design. In this study, we present an integrated framework to support rational formulation design and exploration of optimal dosage regimens. This framework combines population balance-based tablet disintegration and dissolution modeling with physiologically based pharmacokinetic (PBPK) modeling to link critical material attributes (CMAs) with the pharmacokinetic response. The anti-coagulant drug rivaroxaban is selected as a model compound for calibration and deployment of the framework, enabling systematic investigation of the effects of crystal size distribution (CSD) and tablet porosity on in vivo performance. The results demonstrate that CSD has a pronounced impact on in pharmacokinetics, whereas tablet porosity exhibits a smaller but non-negligible effect. Furthermore, optimization is implemented to identify the optimal dose amount under a given formulation for producing the desired pharmacokinetic profile for average patient group, demonstrating the potential of this framework for the digital design of both drug efficacy and treatment strategies.

Keywords: PBM, PBPK, Optimal Dose regimen

1. INTRODUCTION

The performance of oral solid dosage forms can be critically influenced by formulation attributes such as particle size distribution (PSD) of active pharmaceutical ingredient (API), solubility, excipient type, and porosity of dosage form. These properties collectively governed dissolution behavior and, in turn, oral drug absorption. Although formulation effects on dissolution have been widely studied, formulation development still relies largely on traditional trial-and-error experimentation, resulting in substantial resource demand [1]. The challenge arises from the complex, combined effects of CMAs, and the gap between *in vitro* dissolution and in *vivo* performance [2].

Model-informed formulation development has therefore emerged as an important strategy in order to bridge formulation properties and *in vitro* dissolution with *in vivo* performance. By integrating experimental data with computational approaches, this method provides us an effective tool for understanding properties impact. *In vitro-in vivo* correlation (IVIVC) is one of the most widely used approaches. It involves establishing empirical or semi-empirical relationships between dissolution profiles and absorption kinetics, which is inferred from plasma drug concentration data [3]. Although IVIVC can be useful in certain formulation development contexts, it depends on great amounts of paired in vitro and in vivo data to build robust correlation. It is also typically specific to a given drug, and offers limited mechanistic interpretability.

To address the limitations of IVIVC, hybrid approaches that combine dissolution modeling or IVIVC concepts with physiologically based pharmacokinetic (PBPK) modeling have been introduced. PBPK modeling is a mechanistic modeling approach that predicts drug concentration-time profiles. It is based on mass balance equations defined over structured compartments, which incorporate relevant physiological process and drug-specific physicochemical parameters. Several studies

have integrated PSD–dependent dissolution model with PBPK model. For example, Stefan et al. coupled a Noyes–Whitney–based dissolution model with a PBPK framework to study PSD effects on cilostazol absorption [4]. Pepin et al. incorporated the API PSD into the commercial PBPK software, and demonstrated its application for regulatory support [5]. Although these studies successfully link PSD to in *vivo* performance, there is still a lack of systematic frameworks that can evaluate the combined effect of multiple CMAs on pharmacokinetic response.

This work aims to present a framework that integrates predictive modeling with optimization methods to support both formulation design and the development of dose regimen. A PBM-based dissolution model coupled with a PBPK model is developed. Using this combined model, a preliminary investigation is conducted to evaluate the influence of CSD and tablet porosity on plasma drug concentration for rivaroxaban. Additionally, the dose is optimized to achieve a target pharmacokinetic profile.

2. PROPOSED METHODOLOGY

2.1 The digital design framework

A framework is proposed for the integrated digital design of pharmaceutical formulations and dosing regimen, as illustrated in Figure 1. Within this digital design framework, a hybrid model is developed to predict systemic pharmacokinetics from formulation properties, while optimization approaches can be applied to explore optimal formulation design variables and dosing strategies, either independently or simultaneously.

The hybrid model is developed using a two-stage, sequential integrated strategy. In the first stage, a PBM-based tablet disintegration and dissolution model is independently employed to simulate the dissolution behavior of an immediate-release tablet. This model accounts for the impact of CMAs, including tablet porosity and API PSD. Parameters set a priori represent stomach-specific physiological conditions such as solubility, while adaptive parameters are calibrated using in vitro dissolution data under gastric-relevant conditions. Upon completion of tablet disintegration, the outputs from the first stage, including the dissolved API concentration and PSD, are used as initial conditions for the second stage.

In the second stage, the PBM-based dissolution model is embedded within a PBPK framework to describe the dissolution of remaining API particles in the gastrointestinal (GI) lumens. The PBM models predicts time-dependent dissolved API concentrations which act as state variables governing the absorption rate in the PBPK model. The PBPK model accounts for patient physiology and whole-body absorption, distribution, metabolism, and excretion (ADME). Physiological parameters are obtained from literature or databases, while a subset of adaptive parameters is calibrated using in vivo clinical plasma concentration data.

This two-stage strategy is based on the assumptions that (i) tablet disintegration predominantly occurs in the stomach, and (ii) GI transit after the disintegration is complete. These assumptions are based on the consideration that disintegration occurs rapidly relative to gastrointestinal transit and absorption timescale, thereby, treated as a fast initial process.

2.2 Stage I: The PBM-based tablet dissolution and disintegration model

The PBM-based tablet disintegration and dissolution model, adopted from a previous study [6], describes the temporal evolution of crystal populations in different status. It is formulated using two population balance equations (PBEs): one for the number density of bound crystals within the tablet, $n_{CB}(t,L)$, and one for released crystals $n_{CR}(t,L)$, both as functions of time t and particle size L:

$$\frac{\partial n_{CB}(t,L)}{\partial t} = -S_1(t) n_{CB}(t,L) \tag{1}$$

$$\frac{\partial n_{CR}(t,L)}{\partial t} = -\frac{\partial (n_{CR}(t,L) D_c(t))}{\partial L} + S_1(t) n_{CB}(t,L) \tag{2}$$

Here, $S_1(t)$ denotes the tablet disintegration rate, which is described using the Washburn equation. In Eq. (3), θ represents the contact angle, γ is surface tension, and δ denotes to viscosity of liquid. The effective pore length, L_{eff}, is estimated from cubit root of its total pore volume. Tablet porosity (ε) is correlated with effective capillary radius (r_e) through empirical relationship.

$$S_1(t) = \frac{1}{L_{eff}} \sqrt{\frac{r_e(\varepsilon)\gamma \cos\theta}{2\delta}} \cdot \frac{1}{2\sqrt{t}} \tag{3}$$

$D_c(t)$ represents the Noyes-Whitney based dissolution ra, in which k_c is the dissolution rate constant, C_{API} is the concentration of API, and C_s is solubility:

$$D_c(t) = -k_c\left(1 - \frac{C_{API}}{C_s}\right) \tag{4}$$

The concentration of API dissolved in liquid can be calculated as follows:

$$\frac{dC_{API}}{dt} = -3\rho_c k_v \int_0^\infty L^2 n_{CR}(t,L) D_c(t)\, dL \tag{5}$$

where k_v corresponds to crystal shape factor and ρ_c represents crystal density.

2.3 Stage II: The coupled PBM-PBPK model

The PBPK model represents the human body using multiple anatomically relevant compartments, including: brain, lung, adrenal, thyroid, heart, liver, pancreas, spleen, kidney, skin, fat, skeleton, and the gastrointestinal (GI) tract, which are interconnected through blood flow or gastrointestinal transit. The bronchial is grouped

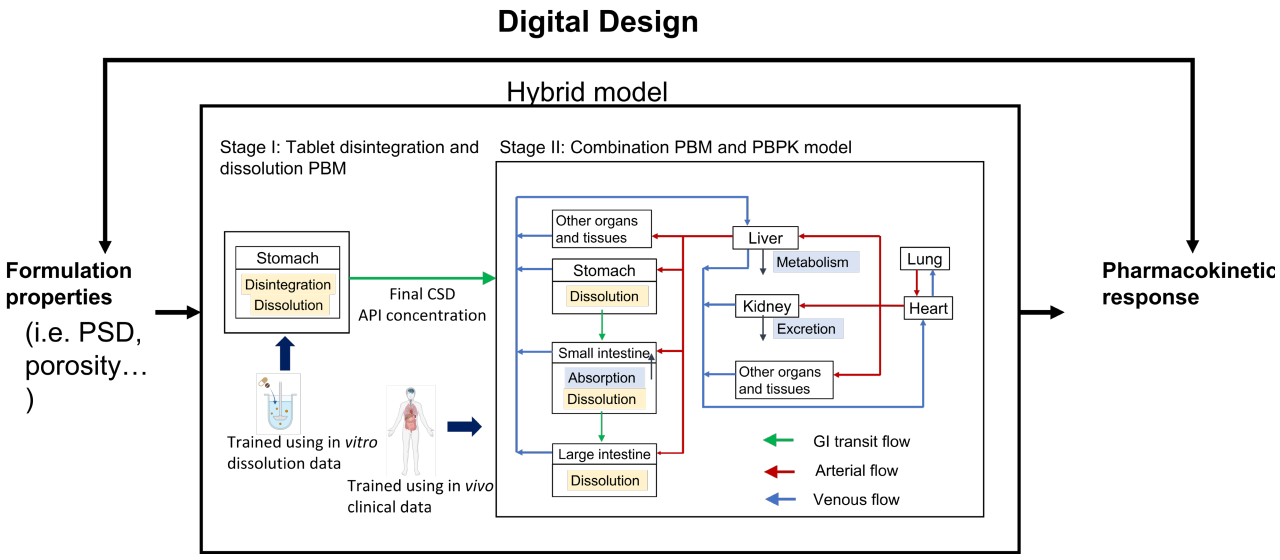

Figure 1. Digital design framework enabling the integrated optimization of drug formulation and dosing regimen design.

within the lung compartment; coronary and heart are unified due to their similar composition. The remaining organs and tissues such as bladder, gonads are lumped into a single compartment because of the low perfusion index (i.e. their minimal blood flow).

Each compartment is divided into three components: plasma, blood cell, and tissue sub-compartments. Drug exchange within a compartment occurs between plasma and blood cells and between plasma and tissue. Under the assumption that GI dissolution and absorption is the rate determining step, intra-compartment drug distribution is assumed to reach rapid equilibrium, thus characterized using partition coefficient K_{eq}^{B} (blood cell-to-plasma) and K_{eq}^{T} (tissue-to-plasma). Only the unbound fraction of drug can across cell membranes freely, thereby participating in the process of intra-compartment transport, metabolism and excretion. Consequently, the unbound plasma drug concentration in compartment i, $C_{u,i}(t)$, is selected as the primary state variable in the PBPK model. The corresponding total plasma drug concentration can be calculated from $C_{u,i}(t)$ using Eq. (6), where f_u is the constant unbound fraction.

$$C_{u,i}(t) = f_u C_i(t) \tag{6}$$

Based on mass-balance principles, the temporal evolution of the unbound plasma drugs in compartment i is governed by convective blood flow transport and can be expressed as:

$$\frac{dC_{u,i}(t)}{dt} = F_{in,i}C_{u,i+1}\varphi_{i+1} - F_{out,i}C_{u,i}\varphi_i \tag{7}$$

Here, $F_{in,i}$ and $F_{out,i}$ denote the volume arterial inflow and venous outflow rates of blood. The weighting factor φ_i is a function of plasma, blood, and tissue volumes as well as the partition coefficients, and is used to calibrate the unbound plasma drug concentration to effective concentration associated blood flow, ensuring consistency in mass-balance calculations.

Three compartments are considered to represent the physiological structure of the GI tract: the stomach, small intestine, and large intestine. Within each compartment, a luminal sub-compartment is introduced to describe intraluminal particle transport, dissolution, and drug absorption. The GI compartments are interconnected through GI transit and systemic blood flow (Figure 2). A single luminal component is used for stomach and large intestine. However, small intestine lumen is subdivided into three segments — duodenum, jejunum, and ileum — to capture regional differences in luminal conditions, including surface area and absorption capacity. Within each luminal segment, a PBE is employed to describe the evolution of API particle size distribution influence by dissolution ($D_c(t)$) and transit flow.

$$\frac{\partial(n_j V_{L,j})}{\partial t} = f_{j-1}n_{j-1-}f_j n_{j-}\frac{\partial(n_j D_c V_{L,j})}{\partial L} \tag{8}$$

where n_j denotes the API number density in j^{th} lumen, f_j and $V_{L,j}$ represents the luminal transit volume flow rate and the liquid volume, respectively.

The luminal liquid phase is assumed to consist primarily of solvent. The luminal liquid volumes of the small and large intestines are assumed to be constant due to bal-anced inflow and outflow. In contrast, the luminal volume of stomach is time-dependent variable because it lacks the upstream gastrointestinal supply. The PBE is coupled with a solute mass balance to describe the mass

of dissolved API ($m_{API,j}$) in each luminal compartment. This accounts for contributions from dissolution and luminal transit. It is noted that for the small intestine lumens, additional drug absorption terms are incorporated to represent systemic uptake:

$$\frac{dm_{API,j}}{dt} = f_{j-1}\frac{m_{API,j-1}}{V_{L,j-1}} - f_j\frac{m_{API,j}}{V_{L,j}} - \int_0^{\infty} k_c\rho_c L^2 n_j D_c V_{L,j}\, dL - P_1 - P_2 \quad (9)$$

Drug absorption is governed by two primary mechanisms: passive and active transport. Passive transport (P_1) is modeled as a permeability-limited flux driven by the concentration gradient across the intestinal membrane. The Passive transport rate is modeled by Fick's law equation, in which permeability (K) is considered. Active transport (P_2) process is mediated by membrane transporters and is modeled using Michaelis–Menten kinetics, where the kinetics is controlled by maximum transport velocity (V_{max}) and protein-drug affinity (K_m).

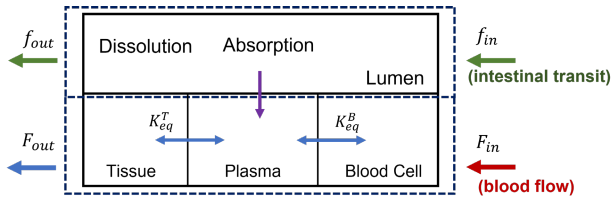

Figure 2. Small intestine compartment scheme.

Drug metabolism and excretion are modeled within the liver and kidney compartments, respectively. Since the hepatic metabolism is also an enzyme-mediated bioprocess, it is described using Michaelis–Menten equation. The excretion is considered in the kidney compartment by using the total renal clearance.

2.4 Dose regimen optimization formulation

For this study, the optimization problem is expressed as a non-linear constrained design problem. The objective function is to minimize the integral of the squared deviation between the predicted plasma concentration profile and a desired target concentration. The proper definition can be seen in following equations:

$$\min_x J(x,z,t) \quad (10)$$

$$s.t.\frac{dz}{dt} = f(x,z,t)\; t \in [0,T] \quad (11)$$

$$x_{lb} \le x \le x_{ub}$$

$$g_i(x,z,t) \le 0$$

Eq. (11) represents the combined PBM-PBPK model as a differential-algebraic equation (DAE) system. The decision variable x denotes the dose amount, where x_{lb} and x_{ub} represent the lower and upper bounds, respectively. The treatment horizon T is defined and considered fixed. In this case, the dosing interval is set to a constant value. The constraint equation g_i represent the toxicity limit. This optimization problem is solved using PyNomad.

3. RESULTS AND DISCUSSION

Within this proposed framework, rivaroxaban, an anticoagulant, is selected as the model drugs. Rivaroxaban is classified as Biopharmaceutics Classification System (BCS) class II drug. BCS class II drugs have low solubility and high permeability, for which dissolution is considered to be the rate-determining step for absorption. The PBM-based tablet disintegration and dissolution model is first calibrated using published in vitro dissolution profiles (Figure 3) [7]. These two dissolution profiles were obtained from dissolution tests of commercial rivaroxaban tablet (Xarelto) in fasted-state simulated gastric fluid (FaSSGF) and intestinal fluid (FaSSIF). The parameters that set a *prior* are summarized in Table 1. The parameters of Washburn equation (Eq. (3)) were obtained from literatures [8].

For the input CMAs parameters, the CSD is assumed to follow a Gaussian distribution with a mean size reported in the literature [7], and the tablet porosity is assumed to be 0.85. The two fitted parameters, including dissolution rate constant and effective capillary radius constant, are shown in Table 2. The fitted results (Figure 3) show good agreement between the PBM model predictions and dissolution profiles.

Table 1: Parameters of the disintegration and dissolution PBM set to literature values

Parameter	Description	Value
C_{sg}	Solubility in FaSSGF	0.011mg/mL
C_{si}	Solubility in FaSSIF	0.0121mg/mL
ρ_c	Crystal density	1491 kg/m^3
γ	Surface tension	0.00723 N/m
δ	Liquid viscosity	0.001Pa s
θ	Contact angle	88.2°

Table 2: Estimated parameter for the disintegration and dissolution PBM

Parameter	Description	Value
k_d	Dissolution rate constant	0.039 μm/s
r_e	Effective capillary radius	1509 μm

The corresponding average plasma drug concentration data were obtained from 40 patients under fasted conditions following a single 15-mg dose of rivaroxaban [7]. For PBPK model, the body characteristic parameters were calculated based on an average standard adult BMI value. Cardiac output and tissue mass were taken from published data [9] and rescaled to the reference BMI using allometric relationships.

Blood flow in each compartment is assigned

proportionally to tissue volume while ensuring the total flow matched cardiac output. For drug-specific parameters, tissue-to-plasma partition coefficients (K_eq^T) are predicted using the Rodgers and Rowland model [10], with the compound type set to neutral. The blood-to-plasma partition coefficients (K_eq^B) are set to be 0.8, following previous report [11]. The unbound fraction (f_u) is set as 0.1 [12].

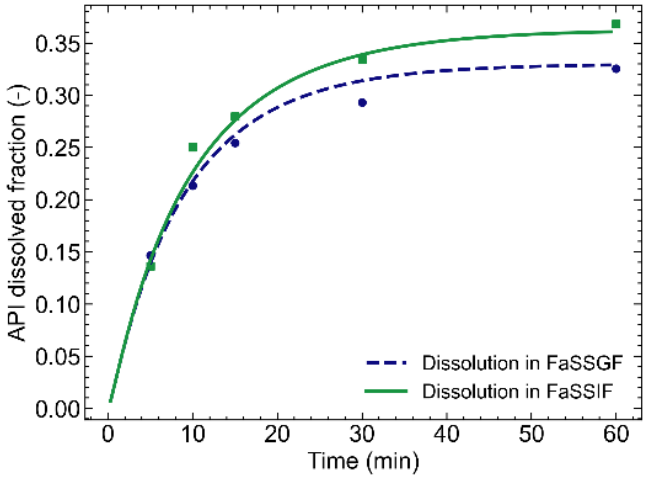

Figure 3. Fitted dissolution profiles under different physiological conditions.

For physiological processes, absorption is assumed to occur solely via passive transport. Given the high permeability of rivaroxaban, passive transport is expected dominate the absorption process. The permeability (K) is set as an adaptive parameter. Hepatic metabolism is modeled using Michaelis-Menten equation, with K_m fixed based on reported value for CYP3A4, which is one of the main enzymes responsible for rivaroxaban metabolism in liver [13]. To prevent overfitting, renal clearance for kidney excretion is also assigned based on literature [12]. The overall estimated model parameters are summarized in Table 3.

Table 3: Estimated parameter of PBPK

Parameter	Description	Value
V_{max}	Maximum velocity	39.5 μg min^{-1} mL^{-1}
K_1	Permeability 1	0.032 min^{-1}
K_2	Permeability 2	0.084 min^{-1}
f_i	Flow rate constant	0.002 min^{-1}

The fitted results (Figure 4) demonstrate that the mean predicted plasma drug concentration profile of rivaroxaban from PBM-PBPK model showed good agreement with the observed data. The predicted area under the curve from the time of administration up to 48 hours (AUC_{0-48h}) is 1667 h μg/L and the (AUC_{0-48h}) for observed data is 1710 h μg/L. The plasma drug concentration increases initially due to dissolution and absorption, reaching a maximum around 2 hr after administration. It then gradually decreases as the metabolism and excretion dominate drug elimination.

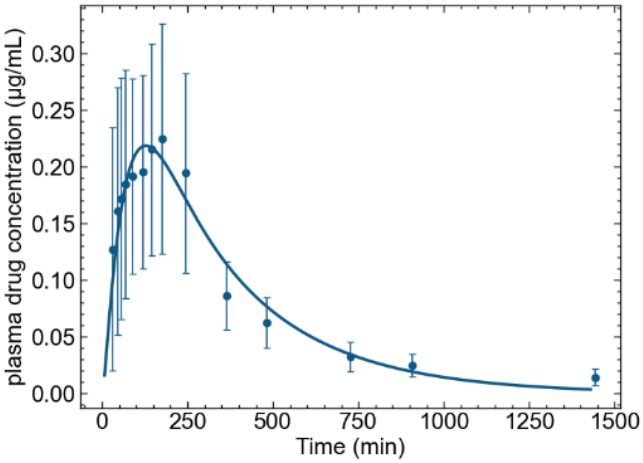

Figure 4. Fitted plasma drug concentration profile.

CSD is considered one of the most impactful tablet properties on dissolution [6], an increase in mean size reduces the dissolution due to the smaller available surface area. This slower dissolution decreases the drug concentration in the intestinal lumen, which in turn lowers the absorption rate. As a result, larger crystal sizes lead to lower maximum plasma concentration and a longer time to reach that maximum (Figure 5(a)). In contrast, tablet porosity primarily influences drug release through disintegration rate. The higher tablet porosity (smaller relative density) results in increased maximum plasma concentration, suggest the impact of initial concentration.

The calibrated model is further employed in the optimization problem. Figure 6 demonstrates the optimal dose regimen, in which the optimal single dose is 20.6 mg adminitered at a dose interval of 4 h over a 24 hr treatment period. In this study, the optimization problem is considered to focus only on the dose amount; however, within the proposed framework, it is possible to consider both the dose regimen and formulation properties. On one hand, the optimal dose regimen can be investigated under a fixed formulation design. On the other hand, a multi-objective optimization problem can be formulated to investigate the minimization of both cost (i.e., the amount of drug) and dosing regimen by considering both dose amount, dosing interval, and formulation properties as decision variables. The therapeutic window can be considered as a constraint not only for the maximum limit but also for the lower limit after the first dose.

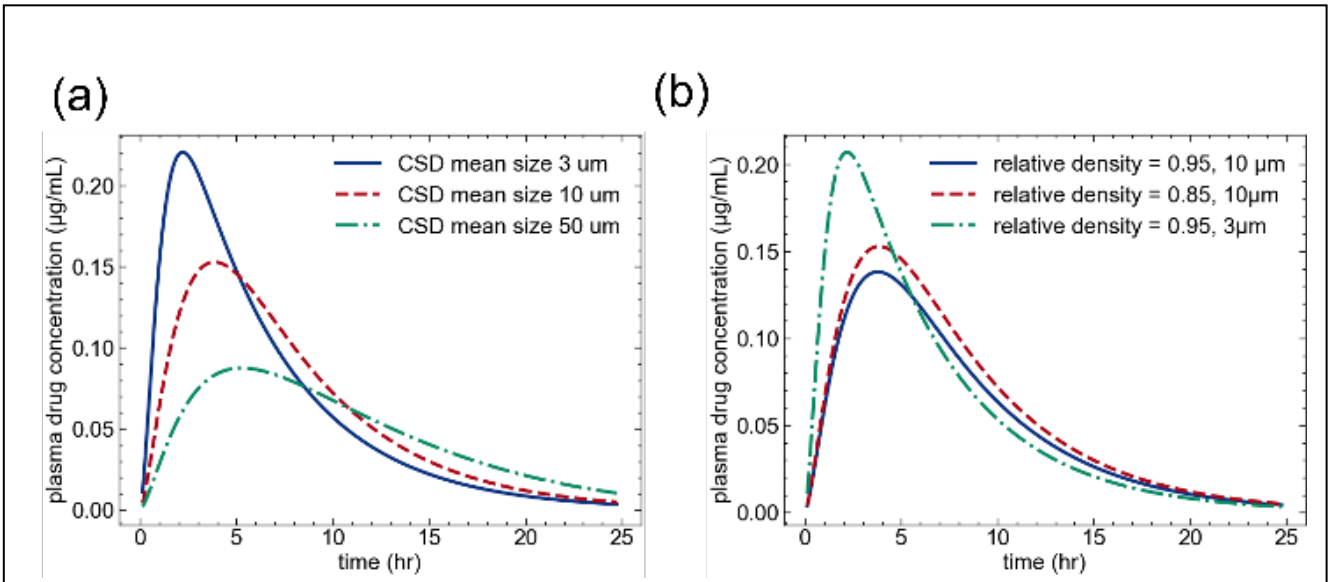

Figure 5. Impacts of (a) CSD and (b) tablet porosity on plasma drug concentrations.

4. CONCLUSION

This work presented an integrated PBM–PBPK digital design framework for rational formulation development and dosing strategy optimization of oral solid dosage forms. By mechanistically linking critical material attributes, including crystal size distribution and tablet porosity, to systemic pharmacokinetics, the framework enables quantitative assessment of formulation–performance relationships beyond traditional approaches. Application to rivaroxaban demonstrated that crystal size distribution has a dominant impact on plasma exposure. Furthermore, optimization of dose amount illustrated the framework's capability to support model-informed dosing decisions, highlighting its potential for data-efficient formulation and regimen design.

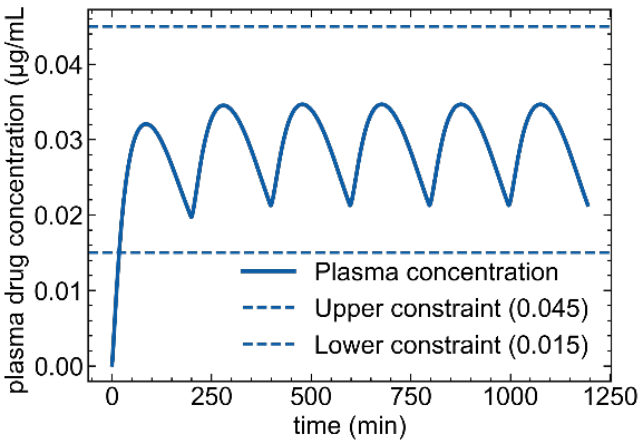

Figure 6. Dose regimen under the optimal dose amount

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REFERENCES

1. Aungst BJ. Optimizing oral bioavailability in drug discovery: an overview of design and testing strategies and formulation options. Journal of Pharmaceutical Sciences 106:921-929 (2017). https://doi.org/10.1016/j.xphs.2016.12.002
2. Zaborenko N, Shi Z, Corredor CC, Smith-Goettler BM, Zhang L, Hermans A, Neu CM, Alam MA, Cohen MJ, Lu X, Xiong L, Zacour BM. First-principles and empirical approaches to predicting in vitro dissolution for pharmaceutical formulation and process development and for product release testing. AAPS J 21: (2019). https://doi.org/10.1208/s12248-019-0297-y
3. Lu Y, Kim S, Park K. In vitro–in vivo correlation: perspectives on model development. International Journal of Pharmaceutics 418:142-148 (2011). https://doi.org/10.1016/j.ijpharm.2011.01.010
4. Willmann S, Thelen K, Becker C, Dressman JB, Lippert J. Mechanism-based prediction of particle size-dependent dissolution and absorption: cilostazol pharmacokinetics in dogs. European Journal of Pharmaceutics and Biopharmaceutics 76:83-94 (2010). https://doi.org/10.1016/j.ejpb.2010.06.003
5. Pepin XJH, Flanagan TR, Holt DJ, Eidelman A, Treacy D, Rowlings CE. Justification of drug product dissolution rate and drug substance

particle size specifications based on absorption PBPK modeling for lesinurad immediate release tablets. Mol. Pharmaceutics 13:3256-3269 (2016). https://doi.org/10.1021/acs.molpharmaceut.6b00497
6. Ma Y, Li W, Liu J, Shang G, Yang H, Gong J, Nagy ZK, Benyahia B. Digital design and optimization of the integrated synthesis and crystallization process using data?driven approaches. AIChE Journal 71: (2025). https://doi.org/10.1002/aic.18931
7. Ishihara M, Kambayashi A. Physiologically based biopharmaceutics modeling to predict bioequivalence of rivaroxaban formulated as conventional tablets, OD tablets, and fine granules. Journal of Drug Delivery Science and Technology 114:107631 (2025). https://doi.org/10.1016/j.jddst.2025.107631
8. Ferdoush S, Gonzalez M. A two-stage mechanistic reduced-order model of pharmaceutical tablet dissolution: population balance modeling and tablet wetting functions. International Journal of Pharmaceutics 664:124635 (2024). https://doi.org/10.1016/j.ijpharm.2024.124635
9. Valentin J. Basic anatomical and physiological data for use in radiological protection: reference values. Ann ICRP 32:1-277 (2002). https://doi.org/10.1016/s0146-6453(03)00002-2
10. Rodgers T, Rowland M. Mechanistic approaches to volume of distribution predictions: understanding the processes. Pharm Res 24:918-933 (2007). https://doi.org/10.1007/s11095-006-9210-3
11. Deepika D, Kumar V. The role of “physiologically based pharmacokinetic model (PBPK)” new approach methodology (NAM) in pharmaceuticals and environmental chemical risk assessment. IJERPH 20:3473 (2023). https://doi.org/10.3390/ijerph20043473
12. Terrier J, Gaspar F, Gosselin P, Raboud O, Lenoir C, Rollason V, Csajka C, Samer C, Fontana P, Daali Y, Reny J, . Apixaban and rivaroxaban's physiologically?based pharmacokinetic model validation in hospitalized patients: a first step for larger use of a priori modeling approach at bed side. CPT Pharmacom & Syst Pharma 12:1872-1883 (2023). https://doi.org/10.1002/psp4.13036
13. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet 53:1-16 (2013). https://doi.org/10.1007/s40262-013-0100-7