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In Silico Evaluation of Abuse-Deterrent Formulation: A Physiologically Based Pharmacokinetic (PBPK) Modeling Approach Using PK-Sim®

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Abstract:
Background: To determine whether an abuse-deterrent formulation can deter drug abuse, it is necessary to evaluate the performance of both intact and tampered dosage forms, both in vitro and in vivo.In this study, Physiologically Based Pharmacokinetic (PBPK) modelling was used to determine a mechanistic in vitro-in vivo relation (PB-IVIVC) and assess the in vivo bioequivalence of intact and tampered formulations.
Methods: PK-Sim® software was used to create a multi-compartmental PBPK model. Reference physiological matrices were used to parameterize a typical healthy virtual human profile. The PBPK model of Bupropion was sourced from the Open Systems Pharmacology (OSP) GitHub repository. Experimental cumulative in vitro dissolution profiles for intact formulations and tampered formulations were incorporated into the model to represent the formulation.
Results: The models accurately outlined plasma concentration-time profiles for both formulations. While the drug is very permeable, the systemic distribution rate is determined by the structural matrix of the dosage forms. The computed geometric mean ratios for C_{max} and AUC remained within the stringent regulatory window of 80.00% to 125.00%, indicating full in silico bioequivalence.
Conclusion: This mechanistic PB-IVIVC framework successfully demonstrates that tampering with the developed abuse-deterrent formulation poses no clinical risk. This computational method proves that the developed ADF has abuse-deterrent properties.

Keywords: PBPK modeling, PK-Sim®, In vitro-in vivo correlation (IVIVC), pharmacokinetics, modeling and simulation

I. Introduction:

The oral route remains the most popular and extensively used method for administration of the drug due to high patient convenience, ease of manufacturing, and affordability [1]. Despite these benefits, developing an efficient oral dosage form is difficult, mainly because of the intricate in vivo absorption, distribution, metabolism, and excretion (ADME) processes that rigidly regulate a drug's systemic bioavailability. Biopharmaceutical Classification System (BCS) class I drugs have high solubility and high permeability, which means that after an immediate release dose, their systemic absorption is usually quick and thorough[2]. However, developing extended-release (ER) dosage forms is essential for active ingredients with narrow safety profiles or a sustained therapeutic window in order to minimize peak-to-trough plasma fluctuations, lower dosing frequency, and lessen potential concentration-dependent side effects [3]. Systemic pharmacokinetics (PK) in an ER delivery system are firmly constrained by the formulation's engineered release rate rather than the drug's innate permeability [4]. In vitro dissolution testing under compendial or biorelevant circumstances has historically been a major component of the evaluation of formulation alternatives as a quality surrogate[5]. However, it can be extremely difficult to accurately estimate whole-body pharmacokinetics from these unprocessed, isolated dissolution time-courses. Traditional in vitro-in vivo correlation (IVIVC) techniques map fraction dissolved to percent absorbed directly using empirical, non-compartmental mathematical deconvolution techniques [6]. Even though they are straightforward, these traditional mathematical models often fail to take into consideration the dynamic, multi-compartmental physiological changes of the human gastrointestinal (GI) tract,

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such as regional transit velocities, variable fluid volume absorptions, and dynamic blood flow rates, which significantly affect the behaviour of a dissolving matrix in vivo[7].

Physiologically-based pharmacokinetic (PBPK) modeling has become a recognized computational approach in modern drug development and regulatory sciences to overcome these limitations [8]. By mathematically dividing the organism into discrete anatomical organ compartments connected by physiological blood flows, PBPK frameworks successfully separate host biology from formulation properties[9].Software packages such as PK-Sim® can perform "mechanistic IVIVC" by combining drug-specific physicochemical data with experimental in vitro dissolution profiles as an input function[10]. This offers a bottom-up, predictive simulation framework that can map how minor variations in in vitro release matrices affect important in vivo clinical metrics.

To curb the widespread public health risks linked with prescription drug abuse, the pharmaceutical industry has emphasized the development of Abuse-Deterrent Formulations (ADFs). ADFs are specialized dosage forms designed with physical, chemical, or pharmacological barriers to prevent product manipulation- such as crushing, chewing, or dissolving- which makes non-intended routes of administration (e.g., insufflation or injection) less rewarding or difficult[11]. To obtain a regulated ADF label claim, global authorities such as the United States Food and Drug Administration (FDA) require a stringent, multi-tiered testing structure. This framework includes Category 1 laboratory-based in vitro tampering and extraction studies to determine how easily a formulation can be defeated, followed by Category 2 in vivo pharmacokinetic (PK) studies to quantify systemic exposure profiles, and finally Category 3 clinical human abuse potential assessments [12]. Within this pipeline, PBPK modeling has emerged as a transformational tool for characterizing and forecasting in vivo behaviour. PBPK models may precisely mimic whole-body plasma concentration profiles by combining mechanical in vitro data (e.g., dissolving rates calculated from intact versus physically crushed matrices) with particular anatomical and physiological gastrointestinal factors. This computational method isolates genuine formulation performance under manipulated conditions, anticipating potential clinical concerns such as quick "dose-dumping" or alterations in absorption kinetics, without depending solely on sophisticated, resource-intensive human testing.In our previous work, we have developed and evaluated an abuse-deterrent formulation using Bupropion hydrochloride as a model drug [13]. The in vitro dissolution profiles of intact and tampered dosage forms were extracted from previously published work [13].

The main objective of this work is to establish a predictive PBPK modeling methodology to quantitatively assess the in vivo pharmacokinetic behavior of two abuse-deterrent formulations (ADF) (Intact and tampered formulations) of Bupropion hydrochloride, a model BCS Class I molecule.The distinct experimental in vitro dissolution characteristics of both formulations will be integrated as mechanistic release inputs using the open-source PK-Sim® modeling software. Our goal is to directly compare the resulting systemic kinetic characteristics, mainly peak plasma concentration, time to peak exposure (T_{max}), and area under the curve, using virtual population simulations. In order to create a bio-predictive model that can expedite formulation optimization before clinical exposure, this comparative in silico technique aims to ascertain if the alternative formulation variations achieve bioequivalence or display unique therapeutic performance windows.

II. Materials and Methods:

The open-source modeling program PK-Sim® (a component of the Open Systems Pharmacology suite, version [Version, 12.2]) was used to develop the PBPK model to forecast and compare the in vivo pharmacokinetic behavior of the two abuse-deterrent formulations.

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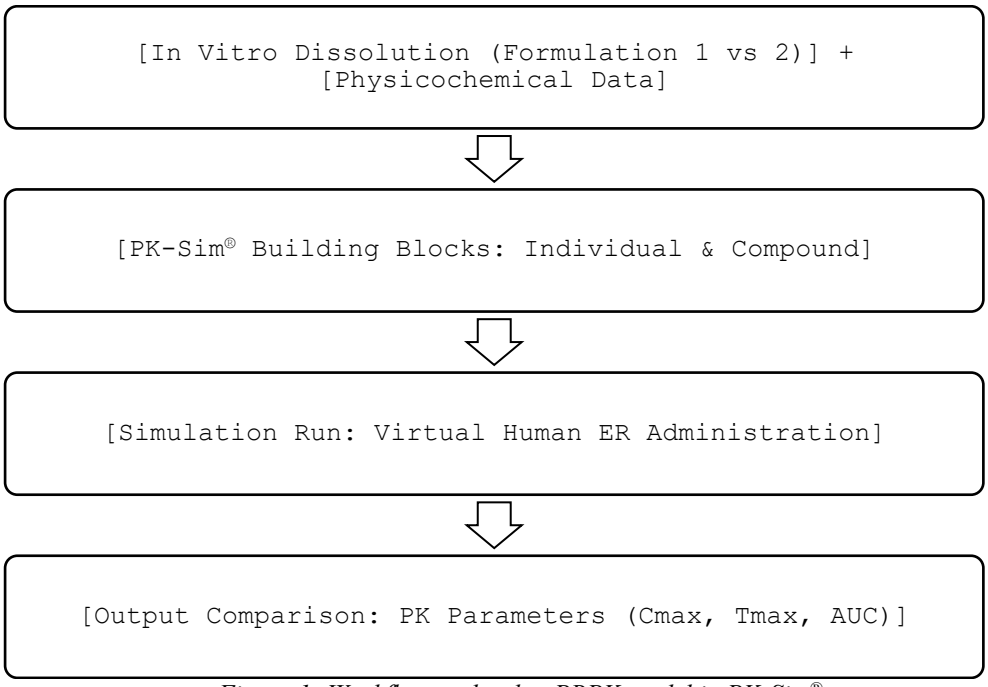

Figure 1: Workflow to develop PBPK model in PK-Sim®

2.1 Software and Computational Framework:
The human anatomy is represented by PK-Sim® using a deterministic, multi-compartmental model in which the volumes, blood perfusion rates, and tissue compositions of each organ are mathematically determined. The integrated Human Intestinal Model, which divides the gastrointestinal (GI) tract from the stomach to the large intestine and takes into consideration regional surface areas, pH profiles, and transit times, is used to determine intestinal transit and regional absorption kinetics.

2.2 Model building block:
The software interface's unique structural building blocks were defined to create the PBPK model.

Virtual Individual/Population:
A typical, healthy virtual person profile was chosen. In accordance with conventional European reference physiological matrices, the demographic attributes were set to a mean age of 30 years, body weight of 73 kg, and body mass index of 23.57·kg/m^2.

Compound Properties:
A whole-body PBPK model for bupropion was implemented using PK-Sim® (version 12.2, Open Systems Pharmacology Suite). The PBPK model for bupropion was obtained from the official Open Systems Pharmacology GitHub repository and is based on the verified model published by Fatima Marok in 2021 [14].
Key physicochemical parameters were maintained as per the validated repository model: molecular weight was set to 239.74 g/mol, lipophilicity (log P) was set to 2.70, and the compound was defined as a weak basic drug with a pKa of 8.75. Cellular permeability was calculated using the PK-Sim standard algorithm. Plasma protein binding was defined with a fraction unbound (fu) of 16% in plasma[15].
Elimination was modeled predominantly via CYP2B6-mediated metabolism to hydroxybupropion. Metabolic clearance was parameterized using specific clearance values scaled to whole-liver CYP2B6 expression[15,16].

2.3. Input of in vitro Dissolution and Formulation Characterization
To serve as the mechanical input for the simulations, in vitro dissolution data for intact and tampered formulations were sourced from the previously published work [13]. Methodological details regarding the dissolution media, apparatus specifications, and analytical quantification are described in depth in that paper. For this PBPK study, the published cumulative release data were utilized as direct input tables within the Open Systems Pharmacology suite to define the formulation-specific release kinetics

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Dissolution Input:
The Table formulation function was used to load the empirical cumulative fraction of drug dissolved over time into the program.

Administration Protocol:
Single-dose oral administrations of identical strengths, 100 mg, were created for both formulations to ensure a direct comparative baseline.

III. Results:

The plasma concentration-time profiles for both formulations following a single oral dose were mapped successfully by predictive simulation.

3.1 Simulated Pharmacokinetic Profiles

The simulated model demonstrated that both formulations have similar plasma concentration-time profiles, despite one being intact and the other being tampered with mechanical tools. The plasma concentration-time profile comparison is shown in Figure 2.

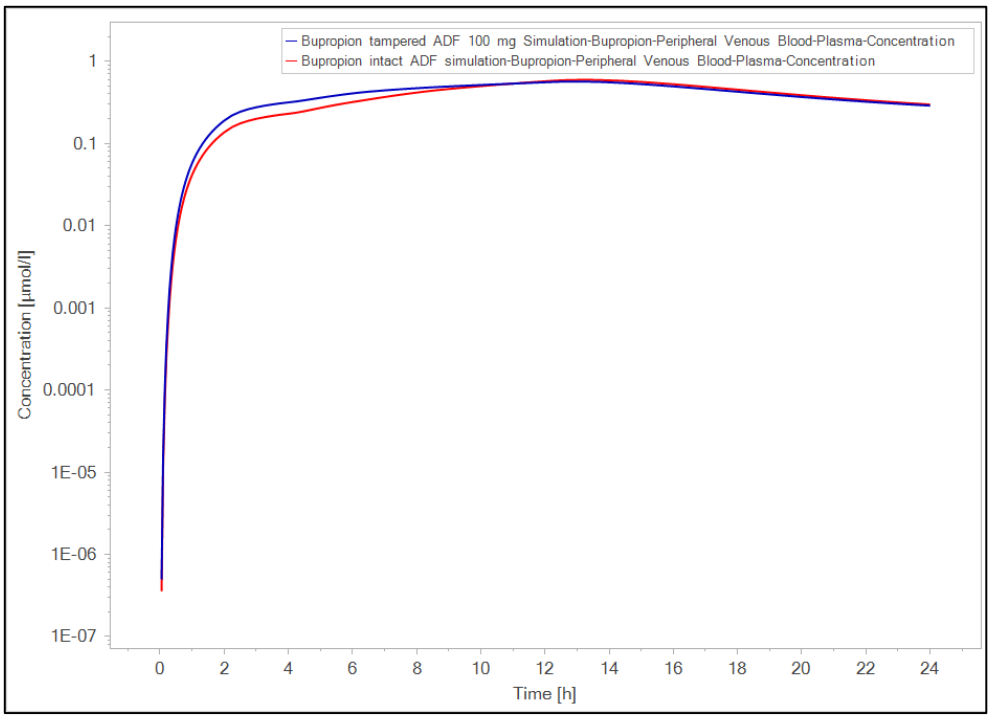

Figure 2: Comparison of simulated plasma concentration-time profiles of intact and tampered ADF

3.2 Comparative Kinetic Parameters

The PK-Sim® simulated charts were used to derive the key pharmacokinetic parameters like peak plasma concentration (C_{max}), time to achieve peak plasma concentration (T_{max}) and area under the curve (AUC). Simulated pharmacokinetic parameters were compared in Table 1. The geometric mean ratio of intact and tampered formulation was calculated to check if its fall within the standard range of bioequivalence.

Table 1: Comparison of simulated pharmacokinetic profiles of intact and tampered ADF

Pharmacokinetic Parameter	Bupropion intact ADF	Bupropion tampered ADF	Geometric Mean Ratio (%) [Intact/Tampered ADF x 100]
C_{max}	594.75 ng/ml	567.33 ng/ml	104.83
T_{max}	13.25 h	13.00 h	101.92
$AUC_{(0-t)}$	553.33 µmol*min/l	571.84 µmol*min/l	96.76
$AUC_{(0-\infty)}$	878.54 µmol*min/l	913.23 µmol*min/l	96.20
$t_{1/2}$	12.59 h	13.65 h	92.23

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3.3 In Silico Bioequivalence Evaluation

The geometric mean ratio of C_{max} and AUC was compared to the standard regulatory bioequivalence limit (80.00% to 125.00%) to determine whether formulation manipulation could result in clinical differences[17].Both formulations are bioequivalent if the ratio falls entirely within the 80-125% window, which proves that tampering with developed ADF does not carry clinical risks. If the ratio is outside the limit, it indicates that tampering with the developed ADF may result in a difference in therapeutic windows or absorption behavior.

IV. Discussion:

The main objective of this investigation was to evaluate whether the minor variation in the in vitro dissolution profile by tampering of ADF results in a clinically significant difference in vivo.We developed a mechanistic in vitro-in vivo connection (PB-IVIVC) to predict whole-body pharmacokinetics by utilizing physiologically-based pharmacokinetic (PBPK) modeling via the open-source PK-Sim® platform. Because their simulated geometric mean ratios for peak plasma concentration (C_{max}) and total systemic exposure (AUC) fell comfortably within the stringent regulatory window of 80.00% to 125.00% established by global authorities, the virtual individual simulations showed that intact ADF and tampered ADF are fully bioequivalent. The PK-Sim® multi-compartmental model demonstrated that these differences are decreased when traveling through the dynamic, shifting geography of the human gastrointestinal tract, despite the fact that in vitro dissolution studies indicated different release rates between the two formulations.

There are significant analytical benefits to using PBPK modeling as a forecasting tool rather than depending only on conventional, empirical mathematical deconvolution. When applied to modified-release formulations, classical IVIVC frameworks frequently fall short of adequately capturing complex absorption dynamics because they approach the human body as an empirical box. On the other hand, PK-Sim® efficiently separates true formulation performance from the biological system by incorporating explicit parameters that reflect actual anatomical blood perfusions and localized gut transit. The U.S. Food and Drug Administration (FDA) is promoting the use of computational models to support biowaivers for formulation modifications and establish clinically relevant dissolution specifications. Our successful confirmation of in silico bioequivalence supports this growing regulatory paradigm and this method significantly reduces post-approval requirement of needless, resource-intensive human bioequivalence investigations.

V. Conclusion:

This study successfully established a robust predictive PBPK modeling workflow in PK-Sim® to map and compare the in vivo behavior of intact and tampered ADFs of a BCS class I drug based only on their in vitro drug release characteristics. The pharmacological bioequivalence of both formulations was confirmed by the computer simulation, which produced matching metrics C_{max}, T_{max}, and AUC that fall securely within conventional regulatory acceptance margins. These results show that clinical effectiveness is not compromised by tampering with developed ADF. It proves that developed ADF has abuse-deterrent potential. In the end, this study demonstrates the potential of open-source PBPK modeling as a dependable, economical tool to assist virtual regulatory submissions, predict bioequivalence, and speed up formulation optimization in contemporary pharmaceutical science.

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