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INTRODUCTION

In silico methods play a crucial role in drug development, enabling researchers to explore complex pharmacokinetic (PK) and pharmacodynamics (PD) behaviors without the need for extensive *in vivo* testing¹. The increasing complexity of drug release profiles necessitates advanced modeling and simulation (M&S) tools that provide accurate, flexible, and scalable solutions². PhysPK® is one such platform designed for precise drug release modeling. However, integrating machine learning (ML) techniques can significantly enhance the predictive power of these models³.

OBJECTIVES

This study aims to implement diverse drug release profiles in PhysPK® and evaluate the efficacy of ML algorithms in optimizing dosage regimens. By combining mechanistic modeling with data-driven approaches, we seek to improve drug formulation strategies and enhance predictive accuracy.

METHODS

To capture a broad spectrum of **drug release models** were developed:⁴

- Zero-order
- First-order
- Higuchi
- Hixson-Crowell
- Korsmeyer-Peppas
- Weibull

Different **machine learning models** were tested to improve dosage predictions and design of modified-release drugs:

- Logistic Regression (LR)
- Artificial Neural Networks (ANN)
- Random Forest Regressor (RFR)
- Decision Tree Regressor, (DTR)
- LightGBM Regressor
- XGBoost Regressor
- K-Neighbors Regressor (KNN)
- Support Vector Regression (SVR)

Key features analyzed:

- Drug release parameters
- PK profiles
- AUC₀₋₂₄, T_{max}, C_{max}, half-life (HL), volume of distribution (V_d), and clearance (Cl)

Model performance was **validated** using:

- Average Fold Error (AFE)
- Absolute Average Fold Error (AAFE)
- Prediction Error (PE)
- Mean Squared Error (MSE)
- Mean Absolute Error (MAE)
- R² score

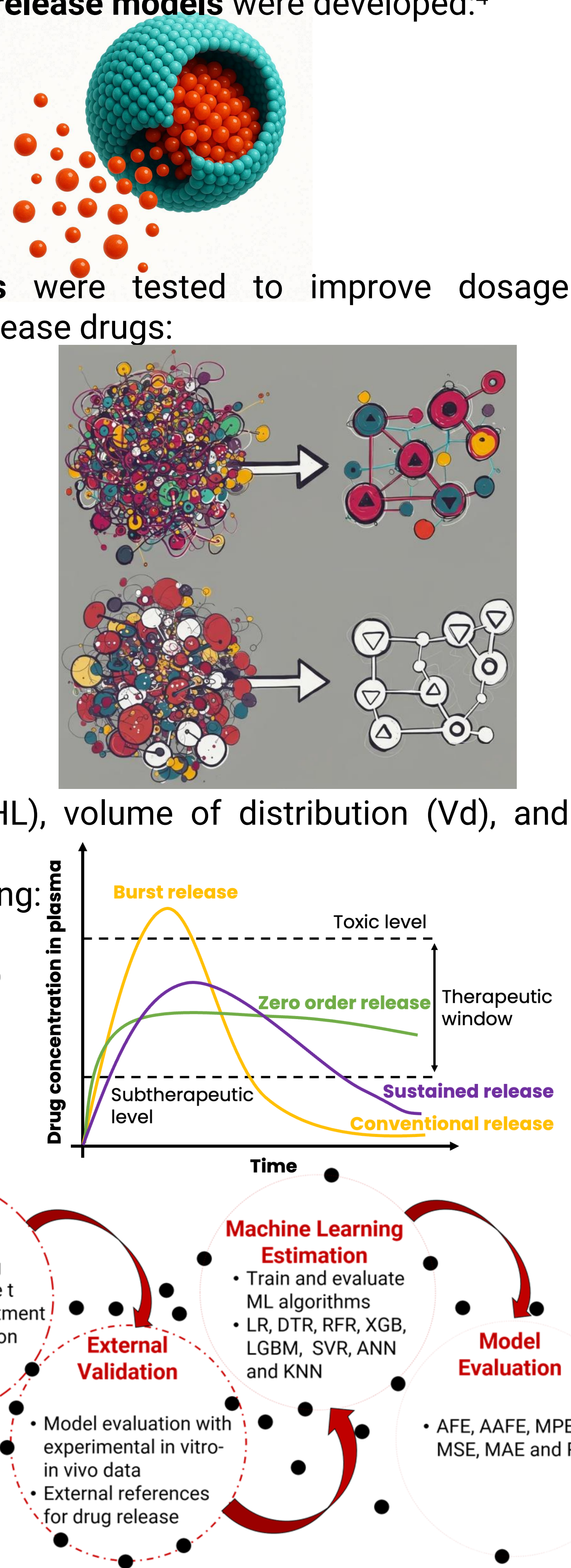


Figure 1. Workflow developing and validating drug delivery systems in PhysPK®

CONCLUSIONS

PhysPK® proves to be a powerful tool for predicting drug release profiles and integrating these predictions into comprehensive PK/PD models. When coupled with ML techniques—particularly XGBoost and LightGBM—PhysPK® achieves superior predictive accuracy and robustness, significantly advancing computational pharmacokinetics.

REFERENCES

- [1] Gruber, Andrea, et al. "Prediction of human pharmacokinetics from chemical structure: combining mechanistic modeling with machine learning." *Journal of Pharmaceutical Sciences* 113.1 (2024): 55-63.
- [2] Peppas, Nicholas A., and Balaji Narasimhan. "Mathematical models in drug delivery: How modeling has shaped the way we design new drug delivery systems." *Journal of Controlled Release* 190 (2014): 75-81.
- [3] Sánchez-Herrero, Sergio, et al. "Embedding R inside the PhysPK Biosimulation Software for Pharmacokinetics Population Analysis." *BIO Integration* 4.3 (2023).
- [4] Dash, Suvakanta, et al. "Kinetic modeling on drug release from controlled drug delivery systems." *Acta Pol Pharm* 67.3 (2010): 217-223.
- [5] Ekenna, Ifeoma Cynthia, and Sunday Okorie Abali. "Comparison of the use of kinetic model plots and DD solver software to evaluate the drug release from griseofulvin tablets." *J. Drug Deliv. Ther* 12.2-S (2022): 5-13.

ECO-FRIENDLY SECTION:



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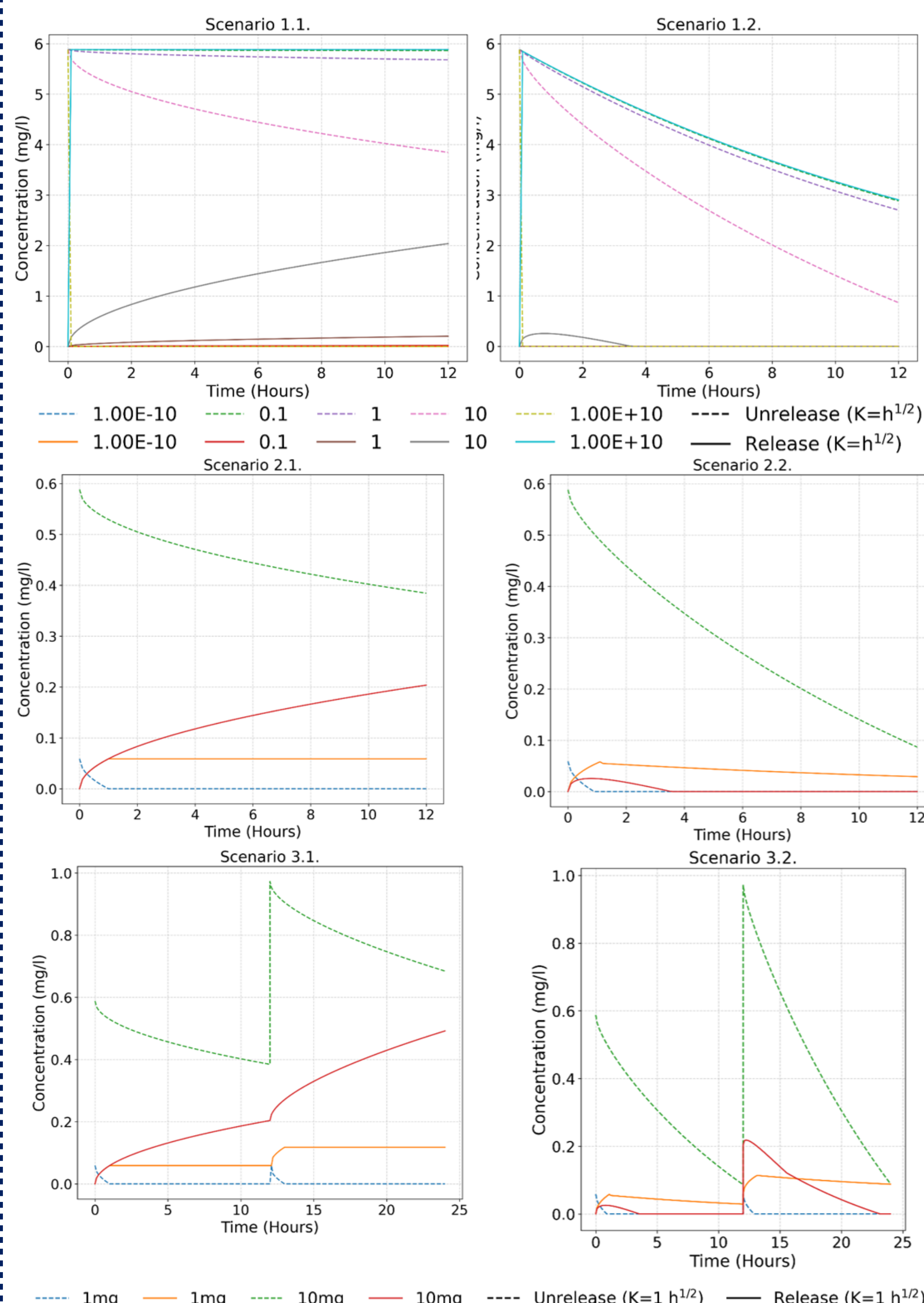
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PAPER ZERO

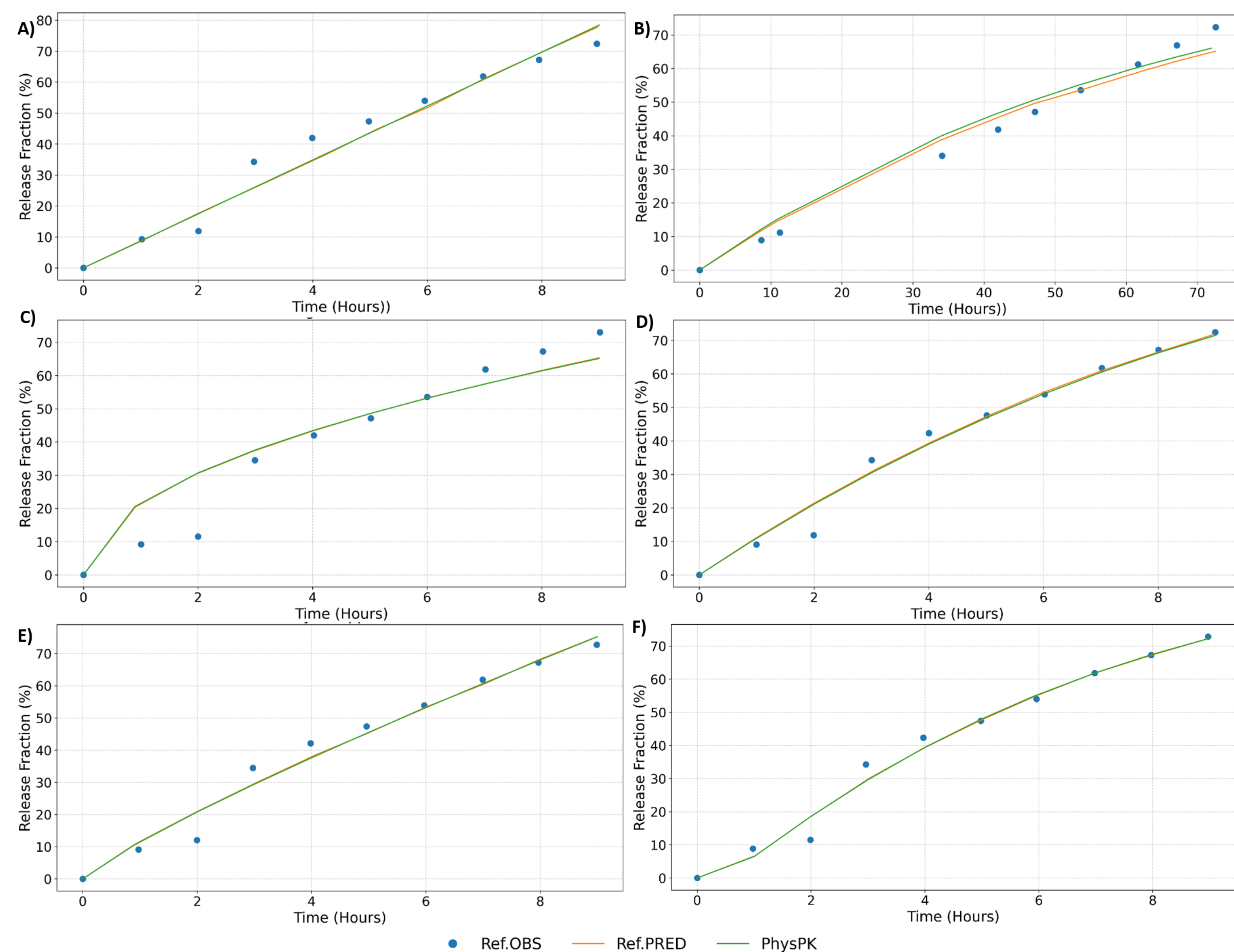
RESULTS (*Only a subset of the results, figures, and tables is presented due to space limitations)

INTERNAL VALIDATION



Example of on of the internal validation results for the First-order drug release mathematical model under different theoretical scenarios. The figure presents concentration-time profiles under different pharmacokinetic conditions: i) Release Constant (K)—Scenarios 1.1 and 1.2 represent drug release and non-release phases without elimination and with linear elimination, respectively; ii) Single-Dose—Scenarios 2.1 and 2.2 show drug release following single-dose administration without elimination and with linear elimination, respectively; and iii) Multi-Dose—Scenarios 3.1 and 3.2 illustrate drug release during multiple-dose administration without elimination and with linear elimination, respectively. The release and non-release rates are determined by the release constant (K, in h^{-1/2}). Concentrations are reported in mg/L, and time is measured in hours. These results validate the mathematical model in drug release behaviour across different dosing and elimination scenarios, emphasizing its applicability in pharmacokinetic modelling.

EXTERNAL VALIDATION



Cumulative release results for the Rutin MSBA complex, obtained through external validation of mathematical drug release models using DD Solver software, following the methodology described in [5]. The curves represent: real experimental data (blue), reference simulation data (orange), and PhysPKR simulation data (green). The external validation confirms the model's accuracy in predicting the release kinetics of the Rutin MSBA complex under specific conditions.

MACHINE LEARNING

ML Model	Zero	First	Higuchi	Hixson-Crowell	Korsmeyer-Peppas	Weibull
LR	[96.18/-22.26]	[14.47/-27.67]	[21.30/-23.88]	[12.43/-26.58]	[98.07/-76.27]	[24.69/-40]
DT	[11.42/-11.31]	[14.06/-11.13]	[16.16/-14.15]	[10.01/-8.97]	[58.15/-67.46]	[17.24/-14.29]
RF	[21.04/-9.55]	[-10.49/13.54]	[15.10/-13.67]	[8.13/-8.76]	[33.20/-31.69]	[22.23/-10.06]
XGBoost	[4.32/-4.88]	[-10.43/9]	[6.28/-4.56]	[8.88/-8.51]	[12.57/-10.53]	[3.74/-2.77]
LightGBM	[41.75/-5.47]	[-6/10.98]	[12.01/-9.00]	[9.20/-6.88]	[24.44/-26.81]	[13.35/-8.9]
SVM	*	*	*	*	*	*
ANN	[19.32/-53.47]	[37.62/-22.43]	[13.55/-10.51]	[6.95/-7.41]	[44.94/-50.79]	[72.8 /-19.21]
KNN	[44.81/-40.67]	[42.81/-56.29]	[41.29/-41.69]	[60.55/-34.68]	[63.28/-48.01]	[44.8/-48.04]

Residual analysis of different ML models and drug release profiles.

*Unsuccessful model