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Table S1. Common values and variability of model parameters for the simulated data in the training dataset.

Variable	Zero Order	First-Order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas	Weibul
Dose (mg/day)	55.95 (+/-25.83)					
CL (l/h)	5.00 (+/-1)					
Distribution (l/h)[3]	7 (0)					
Vc (l)	59.87 (+/-11.99)					
Vp (l)[3]	60 (0)					
K	19.97(+/-7.97)	0.5(+/-0.2)	19.99(+/-7.98)	0.5(+/-0.2)	19.97(+/-7.86)	-
n[4]	-	-	-	-	0.69(+/-0.43)	-
a[5]	-	-	-	-	-	5(+/-2)
b[5]	-	-	-	-	-	0.75(+/-0.3)
Avg. Concentration (mg/ml)	0.24(+/-0.21)	0.24(+/-0.22)	0.21(+/-0.19)	0.27(+/-0.28)	0.23(+/-0.2)	0.21(+/-0.18)
Cmax (mg/ml)	0.63(+/-0.23)	0.63(+/-0.31)	0.53(+/-0.21)	0.97(+/-0.5)	0.55(+/-0.24)	0.45(+/-0.24)
Tmax (h)	2.04(+/-0.97)	2.34(+/-0.59)	3.12(+/-2.07)	4.18(+/-1.82)	2.76(+/-1.88)	4.91(+/-2.22)
HL (h)	17.27(+/-3.87)	17.28(+/-3.87)	17.28(+/-3.87)	17.27(+/-3.86)	17.27(+/-3.86)	17.28(+/-3.87)
AUC0-24 (mg/h/ml)	6.25(+/-2.8)	6.37(+/-3.06)	5.98(+/-2.58)	7.01(+/-3.36)	5.75(+/-2.77)	5.6(+/-2.74)

[1]Number of virtual patients. [2]Data release order model: Zero order, First-Order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull. [3]Fixed value. [4]Korsmeyer-Peppas model input parameters. [5]Weibull model input parameters. Tlag value 0. [6]p-value computed with t-test=1 to show homoscedasticity and normality in all dataset caused by Montecarlo method.

Table S2. Common values and variability of model parameters for the simulated data in the test dataset.

Variable	Zero Order	First-Order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas	Weibul
Dose (mg/day)	55.96 (+/-25.82)					
CL (l/h)	5.00 (+/-1)					
Distribution (l/h)[3]	7 (0)					
Vc (l)	59.87 (+/-12.01)					
Vp (l)[3]	60 (0)					
K	19.97(+/-7.99)	0.5(+/-0.2)	19.99(+/-8)	0.5(+/-0.2)	19.97(+/-7.66)	-
n[4]	-	-	-	-	0.69(+/-0.43)	-
a[5]	-	-	-	-	-	5(+/-2)
b[5]	-	-	-	-	-	0.75(+/-0.3)
Avg. Concentration (mg/ml)	0.24(+/-0.21)	0.24(+/-0.22)	0.21(+/-0.19)	0.27(+/-0.28)	0.23(+/-0.2)	0.21(+/-0.18)
Cmax (mg/ml)	0.63(+/-0.26)	0.63(+/-0.31)	0.53(+/-0.21)	0.97(+/-0.5)	0.55(+/-0.24)	0.45(+/-0.24)
Tmax (h)	2.04(+/-0.97)	2.34(+/-0.59)	3.12(+/-2.07)	4.19(+/-1.82)	2.76(+/-1.88)	4.91(+/-2.22)
HL (h)	17.27(+/-3.87)	17.27(+/-3.86)	17.28(+/-3.87)	17.27(+/-3.87)	17.27(+/-3.87)	17.27(+/-3.86)
AUC0-24 (mg/h/ml)	6.25(+/-2.8)	6.37(+/-3.06)	5.98(+/-2.58)	7.01(+/-3.36)	5.75(+/-2.77)	5.6(+/-2.74)

[1]Number of virtual patients. [2]Data release order model: Zero order, First-Order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull. [3]Fixed value. [4]Korsmeyer-Peppas model input parameters. [5]Weibull model input parameters. Tlag value 0. [6]p-value computed with t-test=1 to show homoscedasticity and normality in all dataset caused by Montecarlo method.

Table S3. Common values and variability of model parameters for the simulated data in the validation dataset.

Variable	Zero Order	First-Order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas	Weibul
Dose (mg/day)	55.99 (+/-25.83)					
CL (l/h)	5.00 (+/-1)					
Distribution (l/h)[3]	7 (0)					
Vc (l)	59.88 (+/-12.00)					
Vp (l)[3]	60 (0)					
K	19.98(+/-7.99)	0.5(+/-0.2)	19.99(+/-8)	0.5(+/-0.2)	19.97(+/-7.98)	-
n[4]	-	-	-	-	0.69(+/-0.42)	-
a[5]	-	-	-	-	-	5(+/-2)
b[5]	-	-	-	-	-	0.75(+/-0.3)
Avg. Concentration (mg/ml)	0.24(+/-0.21)	0.24(+/-0.22)	0.21(+/-0.19)	0.27(+/-0.28)	0.23(+/-0.2)	0.21(+/-0.18)
Cmax (mg/ml)	0.63(+/-0.26)	0.63(+/-0.31)	0.53(+/-0.21)	0.97(+/-0.5)	0.55(+/-0.24)	0.45(+/-0.24)
Tmax (h)	2.04(+/-0.97)	2.34(+/-0.59)	3.12(+/-2.07)	4.19(+/-1.82)	2.76(+/-1.88)	4.91(+/-2.22)
HL (h)	17.27(+/-3.87)	17.27(+/-3.86)	17.28(+/-3.87)	17.28(+/-3.87)	17.27(+/-3.86)	17.27(+/-3.86)
AUC0-24 (mg/h/ml)	6.25(+/-2.8)	6.37(+/-3.06)	5.98(+/-2.58)	7.01(+/-3.36)	5.76(+/-2.77)	5.6(+/-2.74)

[1]Number of virtual patients. [2]Data release order model: Zero order, First-Order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull. [3]Fixed value. [4]Korsmeyer-Peppas model input parameters. [5]Weibull model input parameters. Tlag value 0. [6]p-value computed with t-test=1 to show homoscedasticity and normality in all dataset caused by Montecarlo method.

Table S4. Evaluation of ML models in predicting K (release constants) across different drug-release kinetic models.

ML Model	Metrics Model	Zero	First	Higuchi	Hixson-Crowell	Korsmeyer-Peppas	Weibull
LR	MPE	15.09	15.26	11.93	16.10	25.8	7.77
	AFE	1.07	1.07	1.06	1.08	1.1	1.04
	AAFE	1.37	1.37	1.32	1.37	1.48	1.25
	MSE	59.58	0.04	51.00	0.04	39.3	1.12
	RMSE	7.72	0.20	7.14	0.2	6.27	1.06
	SD(target)	7.99	0.20	8.00	0.20	7.66	2.00
	MAE	5.9	0.15	5.35	0.15	4.6	0.63
	R^2	0.06	0.03	0.22	0.00	0.24	0.47
	Adjusted R^2	0.06	0.03	0.22	0.00	0.23	0.46
DT	MPE	0.26	0.09	0.22	0.01	12.8	8.18
	AFE	1.00	1.00	1.00	1.00	1.05	1.04
	AAFE	1.04	1.02	1.04	1.01	1.31	1.26
	MSE	1.49	0.01	1.25	0.01	12.15	1.34
	RMSE	1.22	0.10	1.12	0.10	3.49	1.16
	SD(target)	7.99	0.20	8.00	0.20	7.66	2.00
	MAE	0.85	0.01	0.75	0.01	1.85	0.67
	R^2	0.98	0.99	0.98	0.99	0.42	0.38
	Adjusted R^2	0.98	0.98	0.97	0.99	0.42	0.37
RF	MPE	0.68	0.37	0.40	0.21	12.23	7.69
	AFE	1.00	1.00	1.00	1.00	1.06	1.04
	AAFE	1.02	1.01	1.01	1.01	1.27	1.23
	MSE	0.94	0.01	0.62	0.01	8.69	0.59
	RMSE	0.97	0.10	0.79	0.10	2.95	0.77
	SD(target)	7.99	0.20	8.00	0.20	7.66	2.00
	MAE	0.39	0.01	0.29	0.01	1.56	0.44
	R^2	0.99	0.99	0.99	0.99	0.56	0.71
	Adjusted R^2	0.99	0.98	0.99	0.99	0.54	0.70
XGBoost	MPE	0.26	0.14	0.16	0.04	10.04	5.22

	AFE	1.00	1.00	1.00	1.00	1.05	1.03
	AAFE	1.01	1.01	1.01	1.01	1.22	1.17
	MSE	0.47	0.01	0.48	0.01	6.1	0.59
	RMSE	0.69	0.10	0.69	0.10	2.47	0.77
	SD(target)	7.99	0.20	8.00	0.20	7.66	2.00
	MAE	0.3	0.01	0.27	0.01	0.23	0.44
	R^2	0.99	0.99	0.99	0.99	0.64	0.71
	Adjusted R^2	0.99	0.99	0.99	0.99	0.64	0.71
LightGBM	MPE	0.12	0.04	0.07	0.03	10.92	5.21
	AFE	1.00	1.00	1.00	1.00	1.05	1.03
	AAFE	1.01	1.01	1.01	1.01	1.24	1.17
	MSE	0.36	0.01	0.37	0.01	6.5	0.59
	RMSE	0.60	0.10	0.61	0.10	2.55	0.77
	SD(target)	7.99	0.20	8.00	0.20	7.66	2.00
	MAE	0.30	0.01	0.28	0.01	1.37	0.44
	R^2	0.99	0.99	0.99	0.99	0.63	0.71
	Adjusted R^2	0.99	0.99	0.99	0.99	0.63	0.71
SVM	*	*	*	*	*	*	*
ANN	MPE	-0.13	0.04	-0.03	0.05	2.9	-0.15
	AFE	1.00	1.00	1.00	1.00	1.01	1.00
	AAFE	1.01	1.01	1.01	1.01	1.08	1.01
	MSE	0.01	0.01	0.02	0.01	2.19	0.01
	RMSE	0.10	0.10	0.14	0.10	1.48	0.10
	SD(target)	7.99	0.20	8.00	0.20	7.66	2.00
	MAE	0.04	0.01	0.05	0.01	0.4	0.03
	R^2	0.99	0.99	0.99	0.99	0.89	0.99
	Adjusted R^2	0.99	0.99	0.99	0.99	0.89	0.99
KNN	MPE	0.46	0.1	0.45	-0.4	12.2	7.12
	AFE	1.00	1.00	1.00	0.99	1.01	1.01
	AAFE	1.05	1.03	1.05	1.03	1.40	1.33
	MSE	4.67	0.01	5.9	0.01	19.13	1.91

	RMSE	2.16	0.10	2.43	0.10	4.37	1.38
	SD(target)	7.99	0.20	8.00	0.20	7.66	2.00
	MAE	1.13	0.1	1.04	0.01	2.36	0.82
	R^2	0.93	0.98	0.92	0.96	0.1	0.1
	Adjusted R^2	0.92	0.97	0.91	0.95	0.1	0.1

*Notes: *Unsuccessful model. LR: Linear Regression; ANN: Artificial Neural Networks; RFR: Random Forest Regressor; DTR: Decision Tree Regressor; LGBM: LGBM Regressor; XGB: XGB Regressor; KNN: K Neighbors Regressor and SVR: Support Vector Regression. AFE: Average Fold Error; AAFE: Absolute Average Fold Error; MPE: prediction error; MSE: Mean Squared Error; RMSE: Root Mean Squared Error; SD(target): Standard deviation of the observed target values (computed on the same evaluation set); MAE: Mean Absolute Error; R^2: R^2 score. Adjusted R^2: adjusted coefficient of determination.*

Table S5. SHAP analysis of different ML models and drug release profiles.

ML Model	**Variables**	**Zero**	**First**	**Higuchi**	**Hixson-Crowell**	**Korsmeyer-Peppas**	**Weibull**
LR	Time (h)	0	0	0	0	0	0
	CL (l/h)	0.08	0.02	1.18	0.01	0.03	0.01
	Avg. Concentration (mg/ml)	0	0	0	0	0	0.15
	Cmax (mg/ml)	1.79	0.07	7.9	0.01	2.83	0.14
	Tmax (h)	0	0.15	4.3	0.13	1.14	0.24
	HL (h)	0	0.01	0.6	0	0.12	0.03
	AUC0–24 (mg·h/ml)	0	0.04	7.9	0.05	0.97	1.05
	Dose	0	0.03	4.6	0.04	0.61	0.87
	Distribution (l/h)	0	0	0	0	0	0
	Vc (l)	0.61	0.06	2.6	0	0.98	0.16
	Vp (l)	0	0	0	0	0	0
DT	Time (h)	0	0	0	0	0	0
	CL (l/h)	6.09	0	0	0	0.52	0.25

	Avg. Concentration (mg/ml)	0	0	0	0	0	0
	Cmax (mg/ml)	1.46	0	4	0	1.31	0
	Tmax (h)	6.09	0.15	5.76	0.15	3.6	0.35
	HL (h)	0	0.02	0	0	0.3	0
	AUC0–24 (mg·h/ml)	0	0	0.3	0	1.28	0.7
	Dose	2.22	0	1.8	0	1.41	0.8
	Distribution (l/h)	0	0	0	0	0	0
	Vc (l)	0.08	0.04	1.59	0.01	0.6	0.2
	Vp (l)	0	0	0	0	0	0
RF	Time (h)	0	0	0.01	0.01	0	0
	CL (l/h)	0.01	0	0.19	0	0	0.02
	Avg. Concentration (mg/ml)	0	0	0.16	0.01	0	0
	Cmax (mg/ml)	0.14	0.01	2.6	0	0.2	0.25
	Tmax (h)	0.57	0.13	4.5	0.13	0.15	0.2
	HL (h)	0.01	0.02	0.27	0	0	0
	AUC0–24 (mg·h/ml)	0.09	0	0.97	0	0.6	0.8
	Dose	0.1	0.01	0.46	0	0.4	0.7
	Distribution (l/h)	0	0	0	0	0	0
	Vc (l)	0.06	0.03	1.3	0.01	0.2	0.2
	Vp (l)	0	0	0.07	0	0	0
XGBoost	Time (h)	0.12	0	0	0	0	0
	CL (l/h)	0.22	0	0.19	0	0	0.01
	Avg. Concentration (mg/ml)	0.13	0	0.09	0	0	0
	Cmax (mg/ml)	2.34	0.02	2.9	0	0.25	0.3
	Tmax (h)	6.02	0.15	5.7	0.15	0.2	0.25
	HL (h)	0.1	0.03	0.24	0	0	0
	AUC0–24 (mg·h/ml)	0.98	0	0.83	0	0.7	0.9
	Dose	1.74	0.02	1.7	0	0.5	0.8

	Distribution (l/h)	0	0	0	0	0	0
	Vc (l)	1.4	0.05	1.8	0.01	0.25	0.3
	Vp (l)	0	0	0	0	0	0
LightGBM	Time (h)	0	0	0	0	0	0
	CL (l/h)	0.12	0	1.19	0	0	00.1
	Avg. Concentration (mg/ml)	0.01	0	0	0	0	0
	Cmax (mg/ml)	1.89	0.01	3.72	0	0.3	0.35
	Tmax (h)	6.37	0.15	5.84	0.15	0.25	0.3
	HL (h)	0.08	0.3	0.17	0	0	0
	AUC0–24 (mg·h/ml)	1.08	0	0.67	0	0.8	1
	Dose	2.51	0.01	1.42	0	0.6	0.9
	Distribution (l/h)	0	0	0	0	0	0
	Vc (l)	1.52	0.44	1.87	0.01	0.3	0.5
	Vp (l)	0	0	0	0	0	0
SVM	*	*	*	*	*	*	*
ANN	Time (h)	0	0	0	0	0	0
	CL (l/h)	0.54	0.02	0.7	0.01	0.03	0.01
	Avg. Concentration (mg/ml)	0	0	0	0	0	0
	Cmax (mg/ml)	2.67	0.03	4.3	0.03	1	0.5
	Tmax (h)	10.78	10.78	5.2	0.01	1.2	0.4
	HL (h)	0.21	0	0	0	0	0
	AUC0–24 (mg·h/ml)	5.9	5.9	0.04	0.05	1	0.9
	Dose	0.86	0	0	0	0	0.6
	Distribution (l/h)	0	0	0	0	0	0
	Vc (l)	2.14	0	0	0	0	0.2
	Vp (l)	0	0	0	0	0	0
KNN	Time (h)	0	0	0	0	0	0
	CL (l/h)	0.5	0.02	0.7	0.02	00.4	0.02
	Avg. Concentration	0	0	4	0	0	0

	(mg/ml)						
	Cmax (mg/ml)	2.3	0.03	5.4	0.02	1.2	0.8
	Tmax (h)	5.5	5.5	0	0.01	1.1	0.7
	HL (h)	0	0	0	0	0	0
	AUC0–24 (mg·h/ml)	2.12	2.12	0.03	0.05	0.9	0.9
	Dose	0	0	0	0	0	0.7
	Distribution (l/h)	0	0	0	0	0	0
	Vc (l)	1.1	0	0.1	0	0	0.2
	Vp (l)	0	0	0	0	0	0

*Notes: *Unsuccessful model. LR: Linear Regression; ANN: Artificial Neural Networks; RFR: Random Forest Regressor; DTR: Decision Tree Regressor; LGBM: LGBM Regressor; XGB: XGB Regressor; KNN: K Neighbors Regressor and SVR: Support Vector Regression.*

Table S6. Residual analysis of different ML models and drug release profiles.

ML Model	**Zero**	**First**	**Higuchi**	**Hixson-Crowell**	**Korsmeyer-Peppas**	**Weibull**
LR	[-14.61/51.98]	[-0.39/1.54]	[-12.49/65.52]	[-0.4/1.56]	[-1.32/4.32]	[-6.07/12.37]
DT	[-17.83/23.85]	[-0.23/0.25]	[-14.59/23.3]	[-0.3/0.09]	[-3.42/4.36]	[-12.15/12.74]
RF	[-8.05/27.12]	[-0.1/0.57]	[-4.69/33.05]	[-0.21/0.6]	[-1.34/4.06]	[-4.79/11.3]
XGBoost	[-17.42/21.3]	[-0.26/0.54]	[-16.41/38.02]	[-36/0.6]	[-1.95/3.89]	[-4.35/9.71]
LightGBM	[-19.4/20.64]	[-0.25/0.52]	[-9.81/36.78]	[-0.21/0.59]	[-1.75/3.83]	[-4.03/10.56]
SVM	*	*	*	*	*	*
ANN	[-1.75/3.13]	[-0.03/0.03]	[-3.74/13.54]	[-0.02/0.04]	[-1.6/3.88]	[-1.14/6.6]
KNN	[-19.3/33.41]	[-0.27/0.65]	[-32.76/53.96]	[-0.61/0.86]	[-3.66/3.72]	[-11.5/13]

*Notes: *Unsuccessful model. LR: Linear Regression; ANN: Artificial Neural Networks; RFR: Random Forest Regressor; DTR: Decision Tree Regressor; LGBM: LGBM Regressor; XGB: XGB Regressor; KNN: K Neighbors*

Regressor and SVR: Support Vector Regression.

Supplementary Material

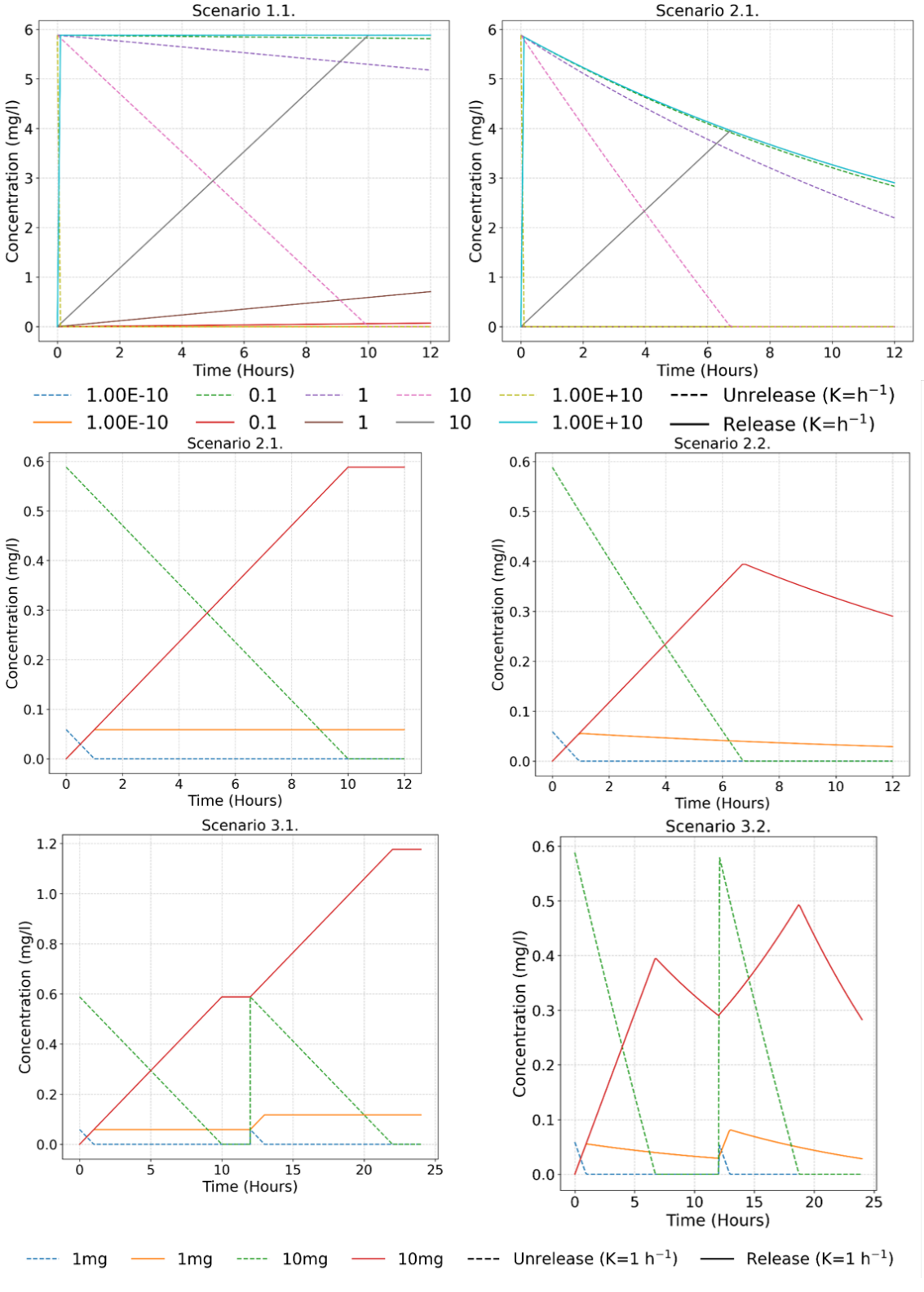
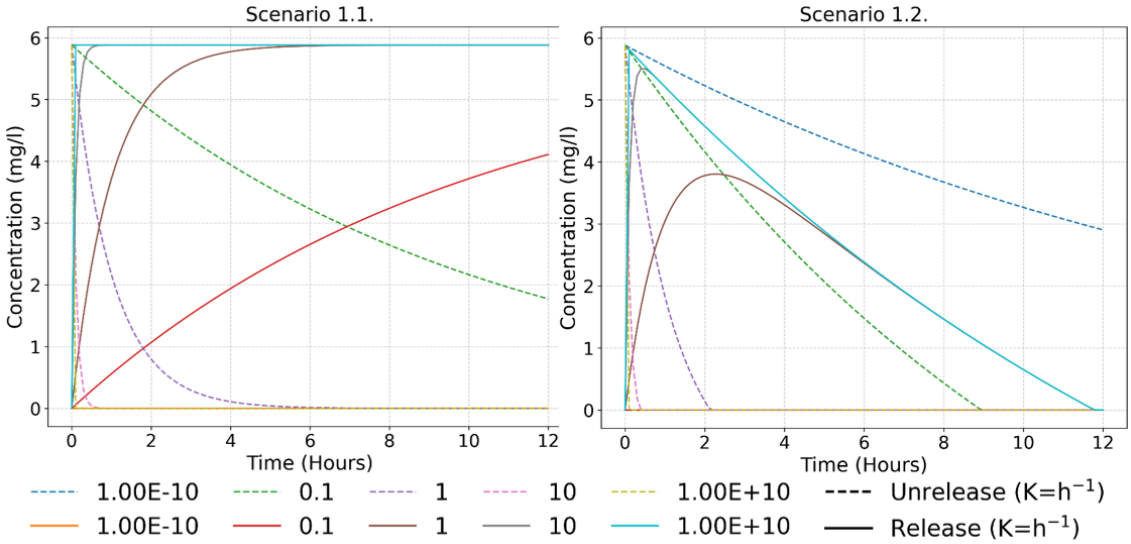


Figure S1. Internal validation results for the zero-order drug release mathematical model under different theoretical scenarios. Scenarios are detailed in Table 1.



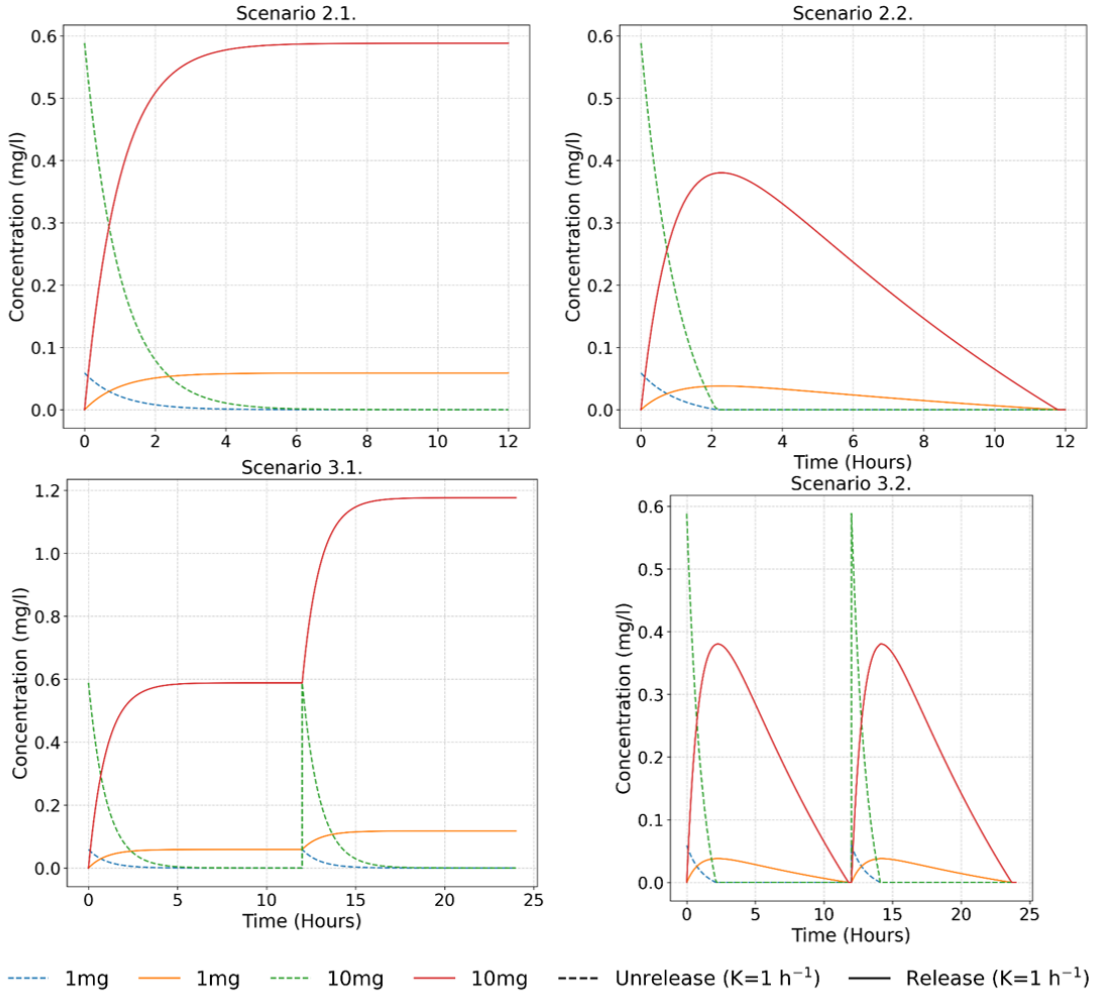


Figure S2. Internal validation results for the First-order drug release mathematical model under different theoretical scenarios. Scenarios are detailed in Table 1.

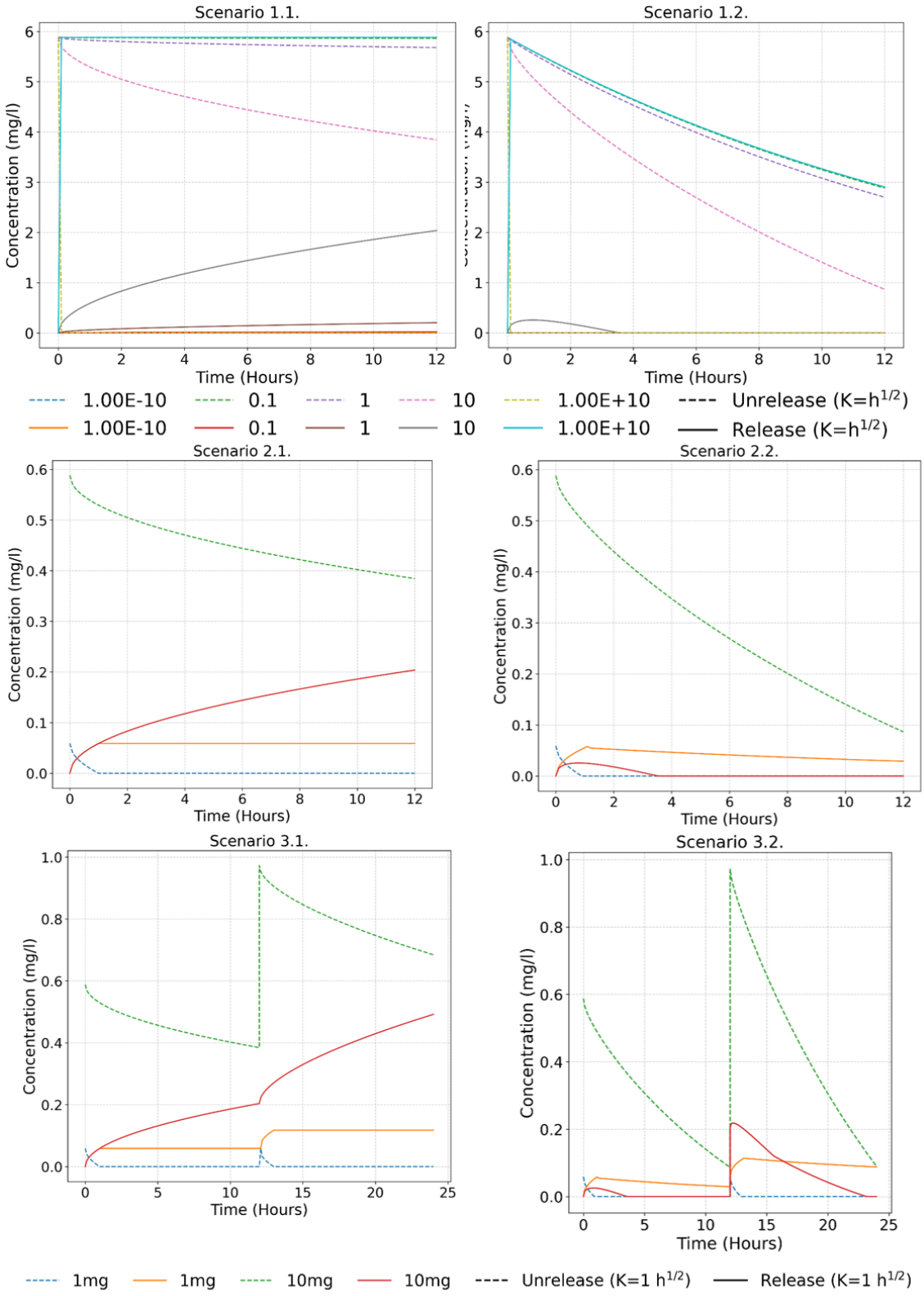


Figure S3. Internal validation results for the Higuchidrug release mathematical model under different theoretical scenarios. Scenarios are detailed in Table 1.

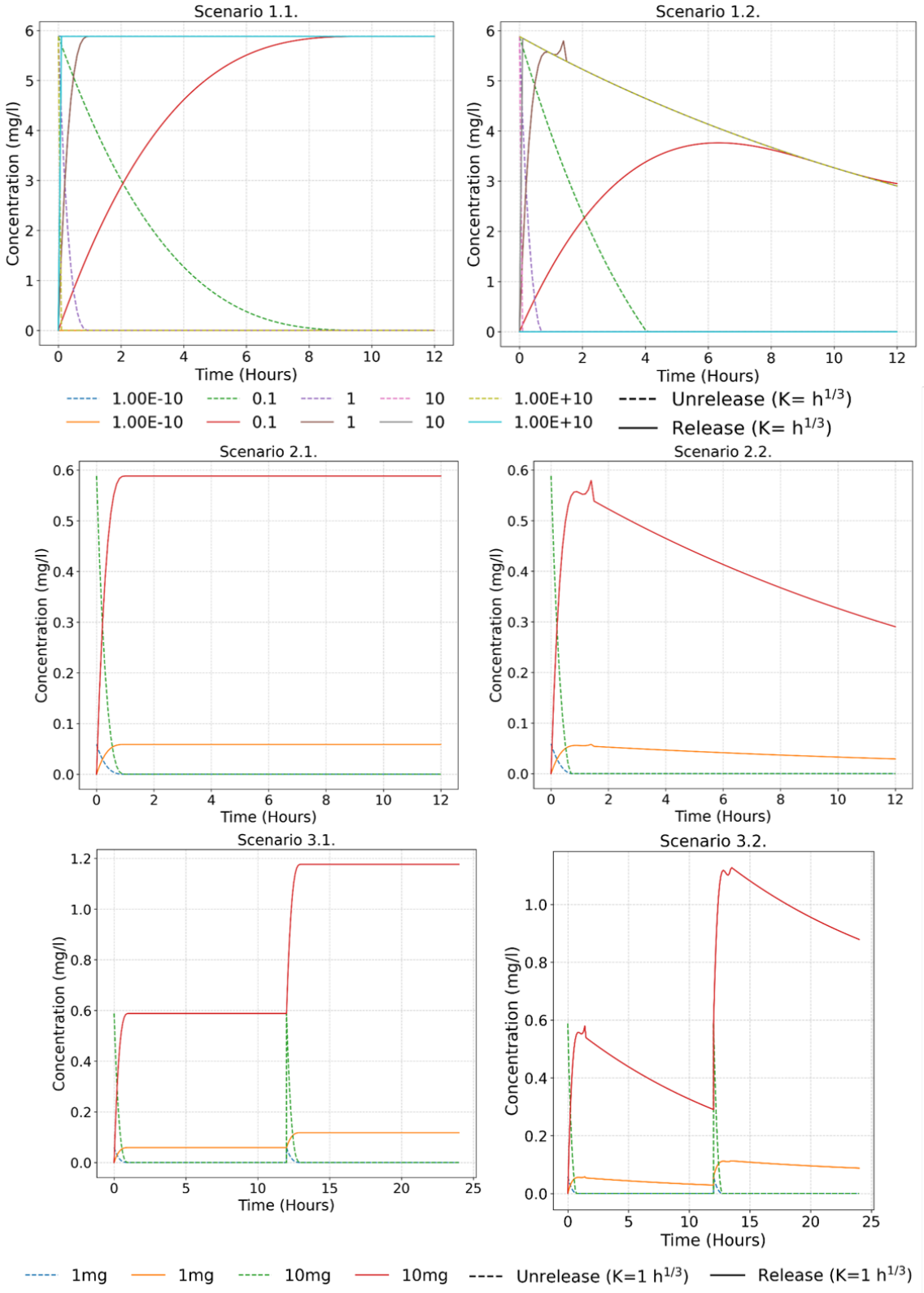


Figure S4. Internal validation results for the Hixson–Crowell drug release mathematical model under different theoretical scenarios. Scenarios are detailed in Table 1.

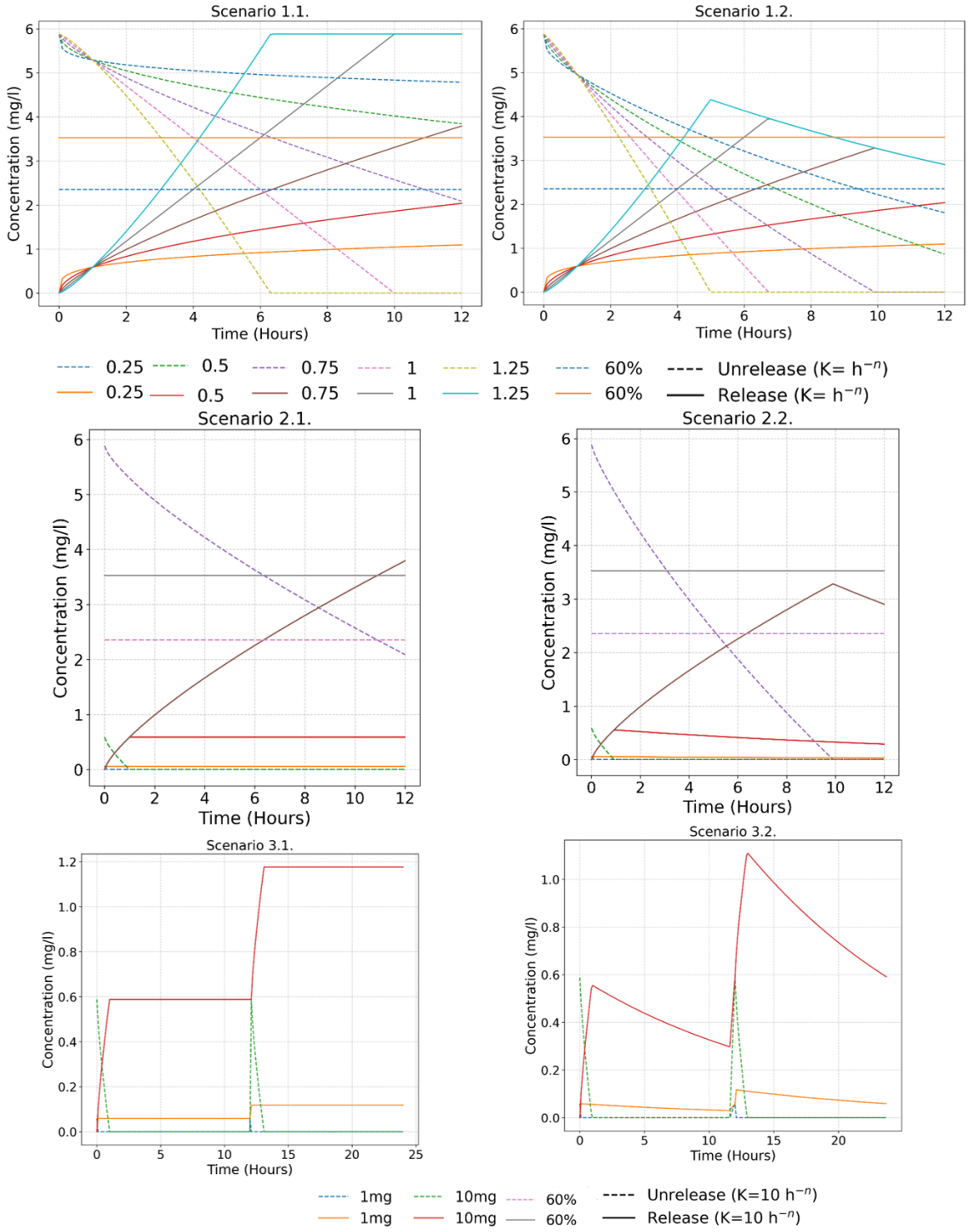


Figure S5. Internal validation results for the Korsmeyer–Peppas drug release mathematical model under different theoretical scenarios. Scenarios are detailed in Table 1.

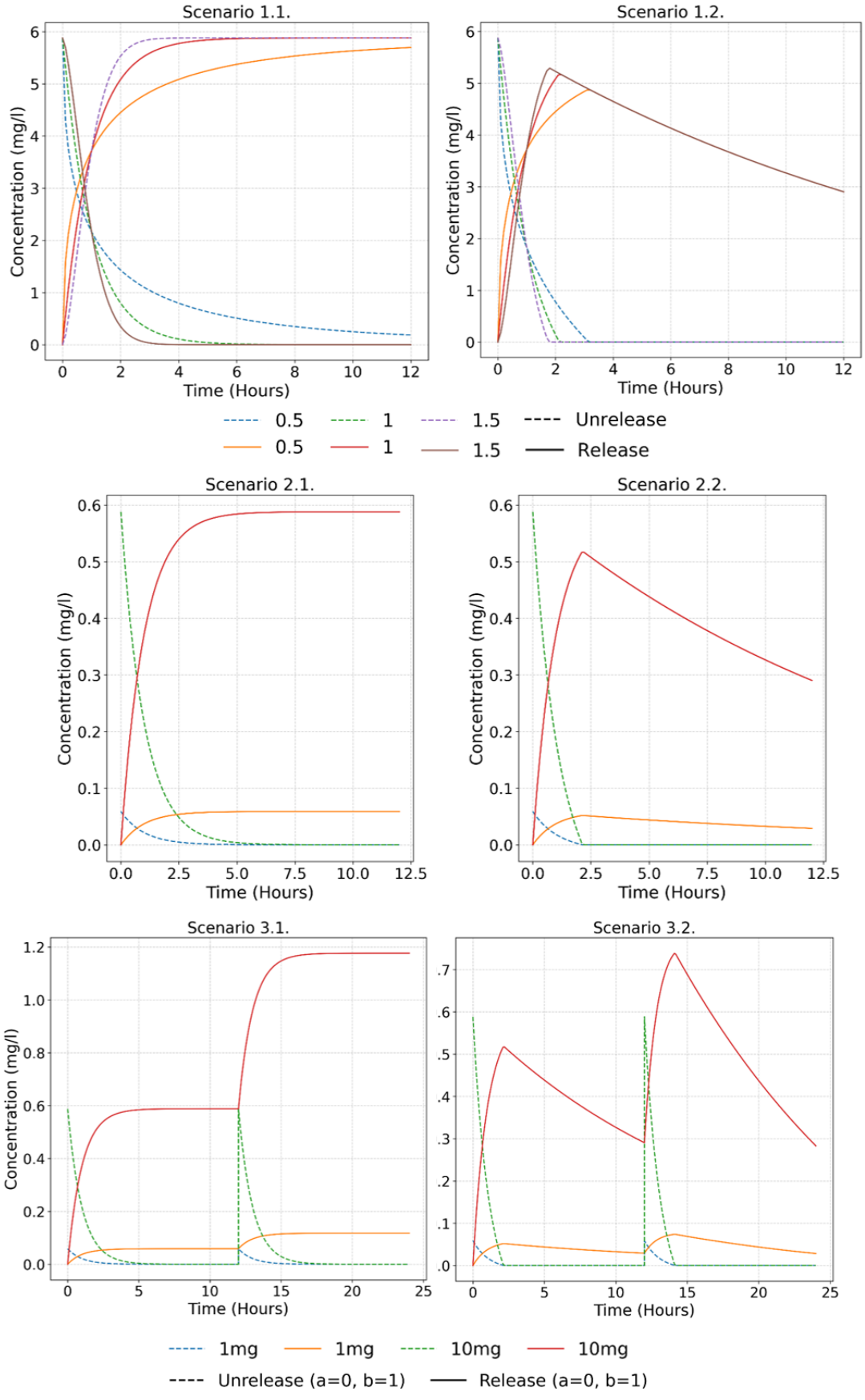


Figure S6. Internal validation results for the Weibulldrug release mathematical model under different theoretical scenarios. Scenarios are detailed in Table 1.

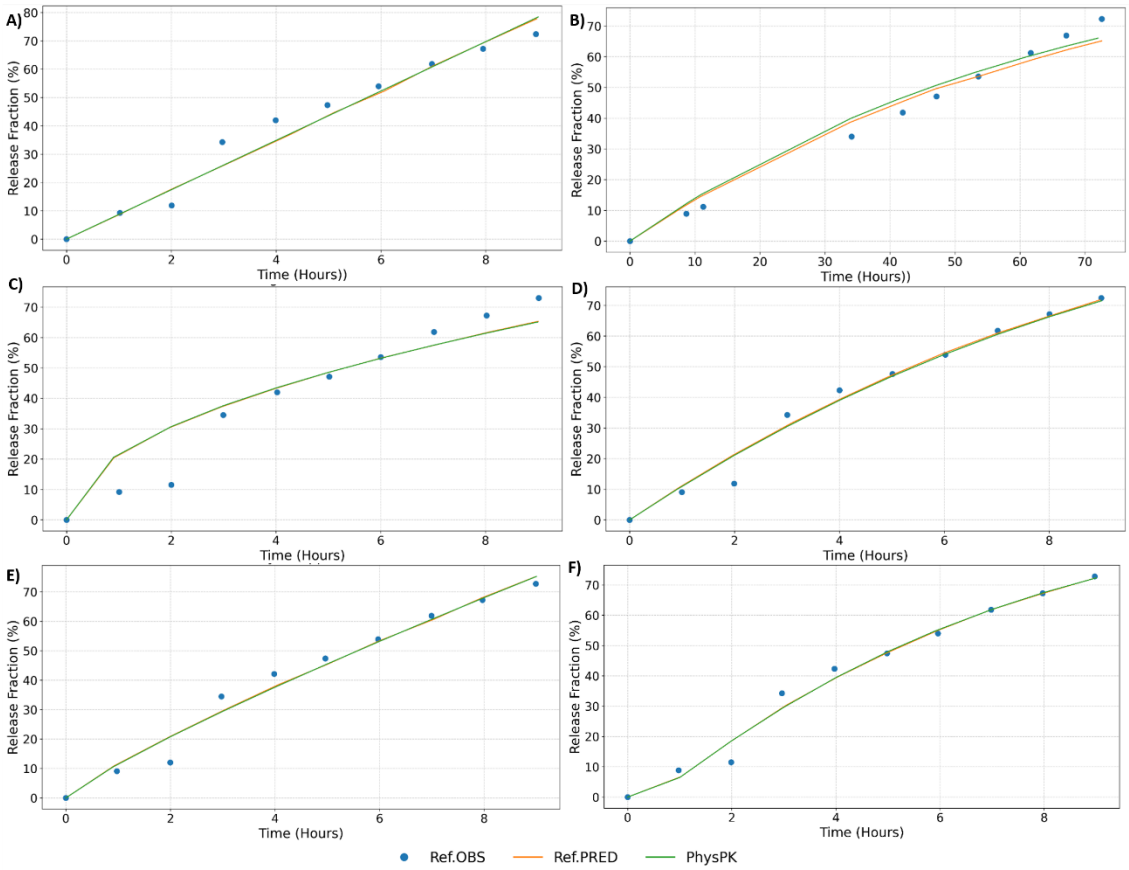


Figure S7. Cumulative release results for the Rutin MSBA (mesoporous SBA-15) complex, obtained through external validation of mathematical drug release models using DD Solver software.[26] The curves represent: real experimental data (blue), reference simulation data (orange), and PhysPK® simulation data (green).

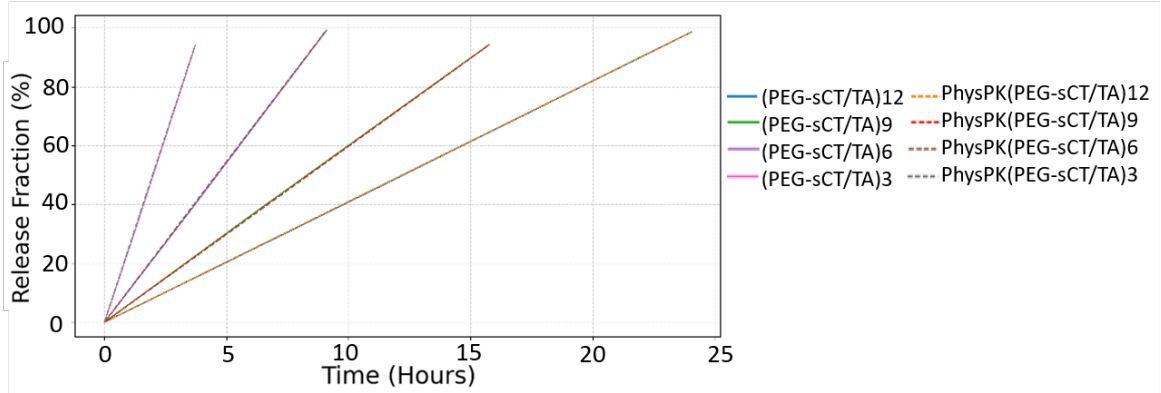


Figure S8. Cumulative release of PEG-sCT from PEG-sCT/TA films with varying bilayer numbers, expressed as a percentage of the total drug released over time. The figure compares the release

kinetics of PEG-sCT/TA films simulated using the model in solid lines.[27] The PhysPK® simulations (dashed lines). The bilayer numbers evaluated are 3, 6, 9, and 12.

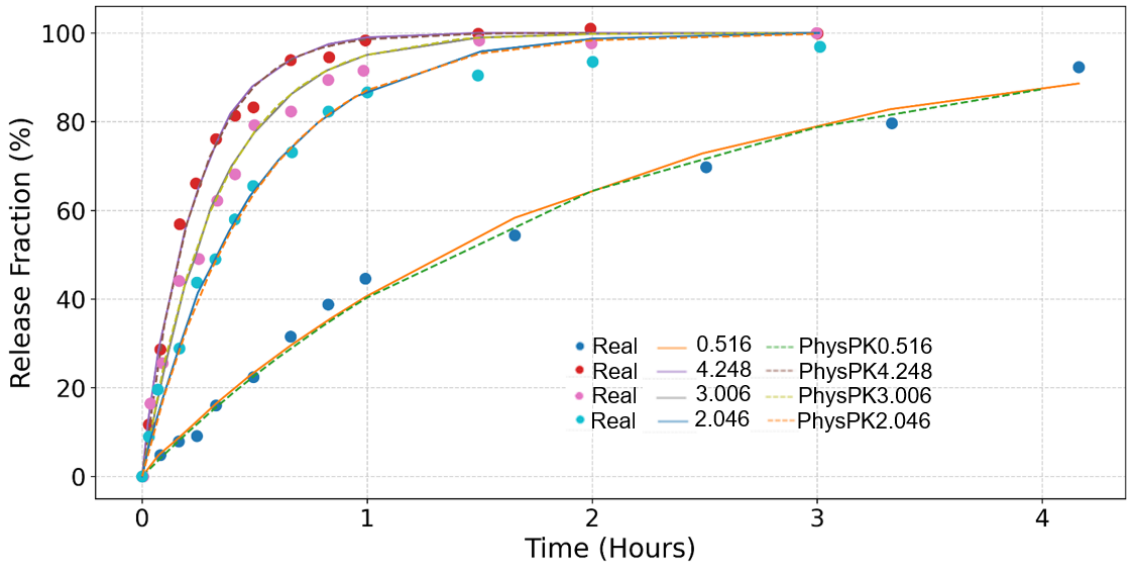


Figure S9. The figure illustrates the release fraction (%) of Ketoprofen from synthesized silica aerogels with different densities (g/cm^3).[28] The dot points represent real experimental data, the solid lines correspond to simulations of Ketoprofen release from silica aerogels at varying densities, and the dashed lines depict PhysPK® simulations.

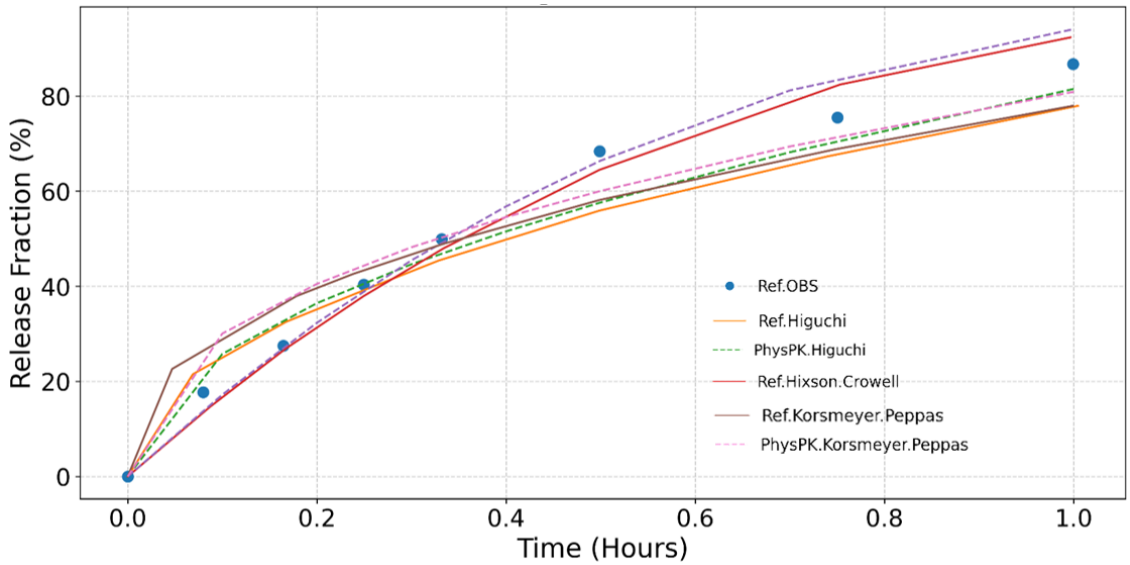


Figure S10. The figure depicts the release fraction (%) over time (hours) of four polyphenols from L. pumila encapsulated in GA:WPI microcapsules under simulated gastric fluid (SGF) conditions: A) Gallic acid, B) Protocatechuic acid, C) Epigallocatechin, and D) Rutin.[29] Dot points: Real data. Solid line:

Ketoprofen silica aerogels for different density (g/cm^3) simulations. Dash lines: PhysPK® simulations.

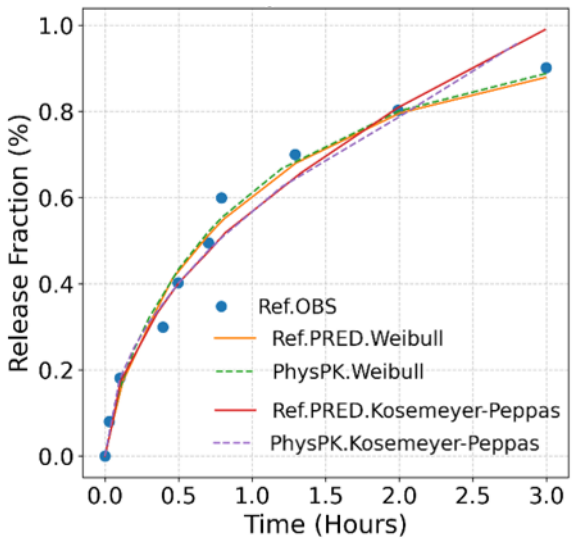


Figure S11. The figure illustrates the controlled release profile of furosemide over time (hours) from a multilayer polyion system composed of 6 gelatin layers at pH 1.4.[30] Dot points represent real experimental data, solid lines correspond to simulations of furosemide release, and dashed lines depict PhysPK® simulations. Two models are compared: Weibull and Korsmeyer-Peppas.