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An investigation into the possibilities and limitations of *in silico* absorption modeling: GastroPlus™ simulation of nimesulide oral absorption

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In Silico Absorption Simulation

Implementation:

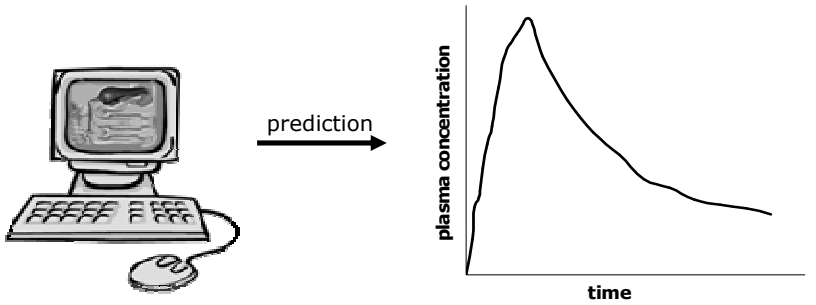
- Formulation development
- Assessment of the influence of drug properties on oral drug absorption
- Prediction of food effects
- Prediction of drug-drug interactions
- Establishment of *in vitro-in vivo* correlation (IVIVC)
- Justification of biowaivers

Gastrointestinal Simulation Technology

(GastroPlus™ software package, Simulation Plus Inc., Lancaster, CA, USA)

- Physiologically based absorption model
- Mathematical model
- Predictive model

  - Physiological parameters of animals or humans
  - Drug physicochemical and pharmacokinetic properties
  - Formulation properties of drug products



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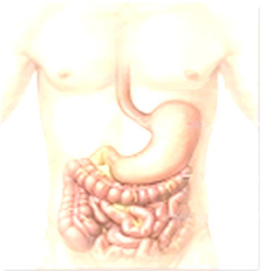
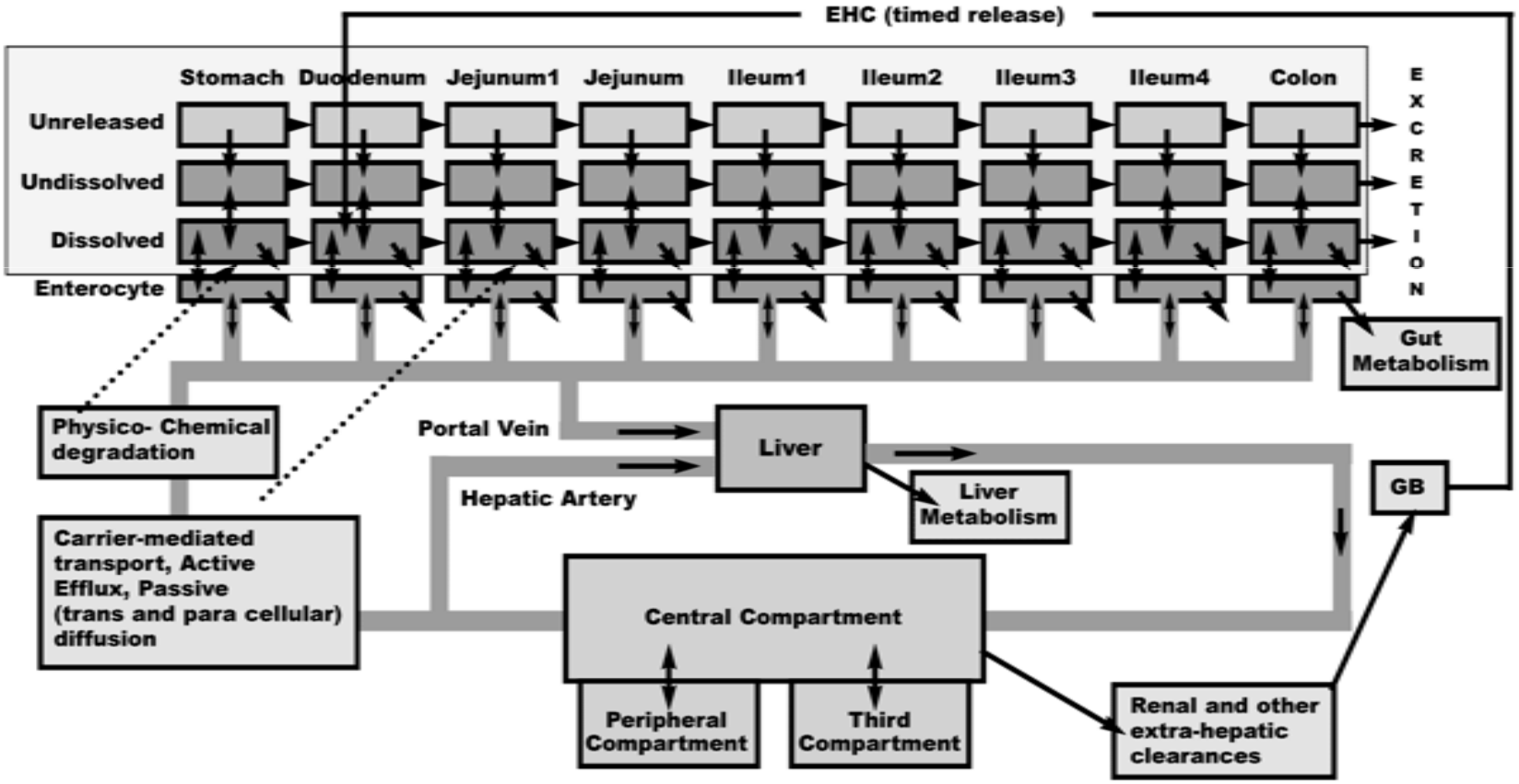
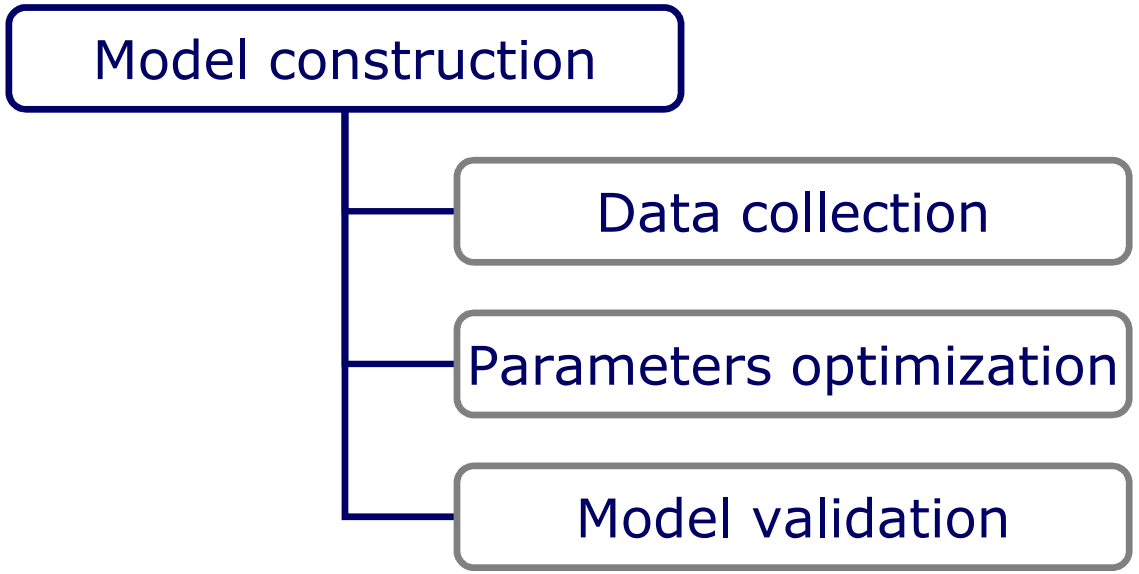


Advanced Compartmental Absorption and Transit Model



GastroPlus Manual, 2008. Simulation Plus Inc., Lancaster, USA

General Modeling and Simulation Strategy



The accurate prediction is often limited by the lack and/or inappropriate selection of reliable input data

Model Drug: Nimesulide (NIM)

- BCS Class II drug
- Highly permeable[a]
- Weak acid; pK_a 6.4[b]
- pH-surfactant-dependent solubility
- Tablet strength 100 mg; recommended dosage: twice daily
- After oral administration, NIM is rapidly and extensively absorbed[c]

[a] Meriani F et al. J Pharm Sci. 2004;93(3):540-52.

[b] Dellis D et al. J Pharm Biomed Anal. 2007;44:57–62;

[c] Bernareggi A. Clin Pharmacokinet. 1998;35:247-74.

Model Presumptions

Model 1

influx transporters in the intestine influence NIM absorption

adjustment of the absorption scale factors (ASFs)

Model 2

pH-surfactant induced increase in NIM solubility *in vivo*

optimization of solubility and permeability values

Summary of NIM Input Parameters

Parameter	Model 1	Model 2
Molecular weight (g/mol)	308.31	
logD (pH 7.4)	1.8[a]	1.48[b]
pK_a	6.4[b]	
Human jejunal permeability (cm/s)	2.225×10^{-4} [c]	1.116×10^{-4} [a] 2.002×10^{-4} [d]
Dose (mg)	100	
Dose volume (ml)	200[e]	
Solubility at pH 4.5 (mg/ml)	0.007[f]	0.017[b] 0.030[d]
Mean precipitation time (s)	900[g]	
Diffusion coefficient (cm^2/s)	0.757×10^{-5} [c]	
Drug particle density (g/ml)	1.2[g]	
Effective particle radius (µm)	25[g] 5[d]	25[g]

Parameter	Model 1	Model 2
Body weight (kg)	88[e]	
First pass extraction in liver (%)	0.1[h]	/
Blood/plasma conc. ratio	0.668[c]	1[g]
Unbound percent in plasma (%)	4.513[c]	3[a]
Clearance (L/h/kg)	0.039[h]	0.028[a]
Volume of distribution (L/kg)	0.226[h]	0.14[a]
Elimination half-life (h)	4.02	3.42
Simulation time (h)	15	
Dosage form	IR tablet	IR suspension/ IR tablet

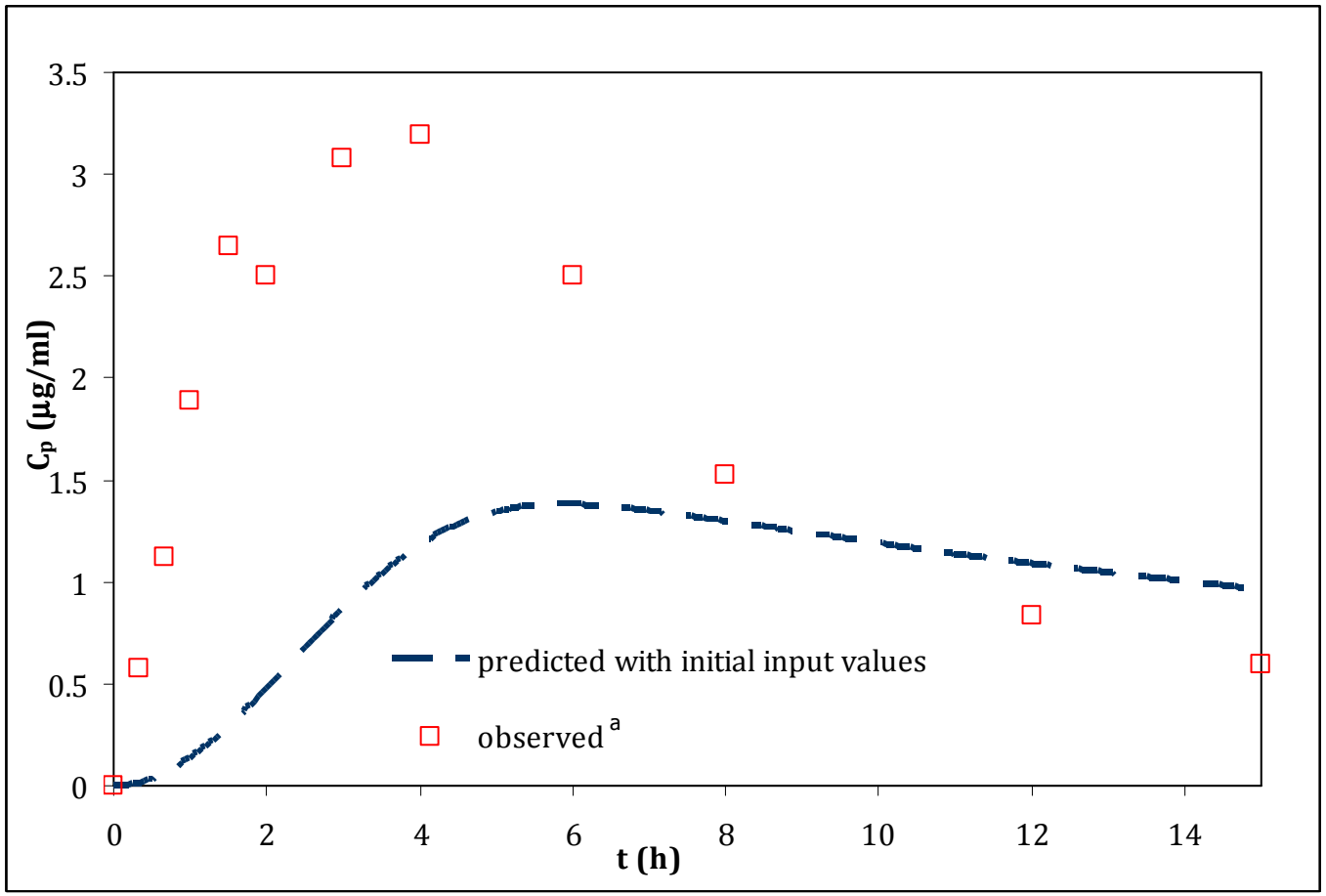
[a] Rainsford KD, ed. Nimesulide: actions and uses. Birkhäuser Verlag; 2005; [b] Dellis D et al. J Pharm Biomed Anal. 2007;44:57–62; [c] *in silico* predicted (ADMETPredictor™ module); [d] optimized values; [e] Jovanovic D et al. Vojnosanit Pregl. 2005;62(12):887–93; [f] Grbic S et al. Drug Dev Ind Pharm. 2009;35(7):852–6; [g] default GastroPlus™ values; [h] Bernareggi A. Clin Pharmacokinet. 1998;35:247-74.

ASF Values Employed

Compartment	Model 1	Model 2 (GastroPlus™ default)
Stomach	0	0
Duodenum	1000	2.687
Jejunum 1	500	2.668
Jejunum 2	2.600	2.633
Ileum 1	0.500	2.588
Ileum 2	0.500	2.551
Ileum 3	5.547	2.460
Caecum	6.098	1.328
Asc colon	12.240	1.995

Model 1: Initial Simulation Results...

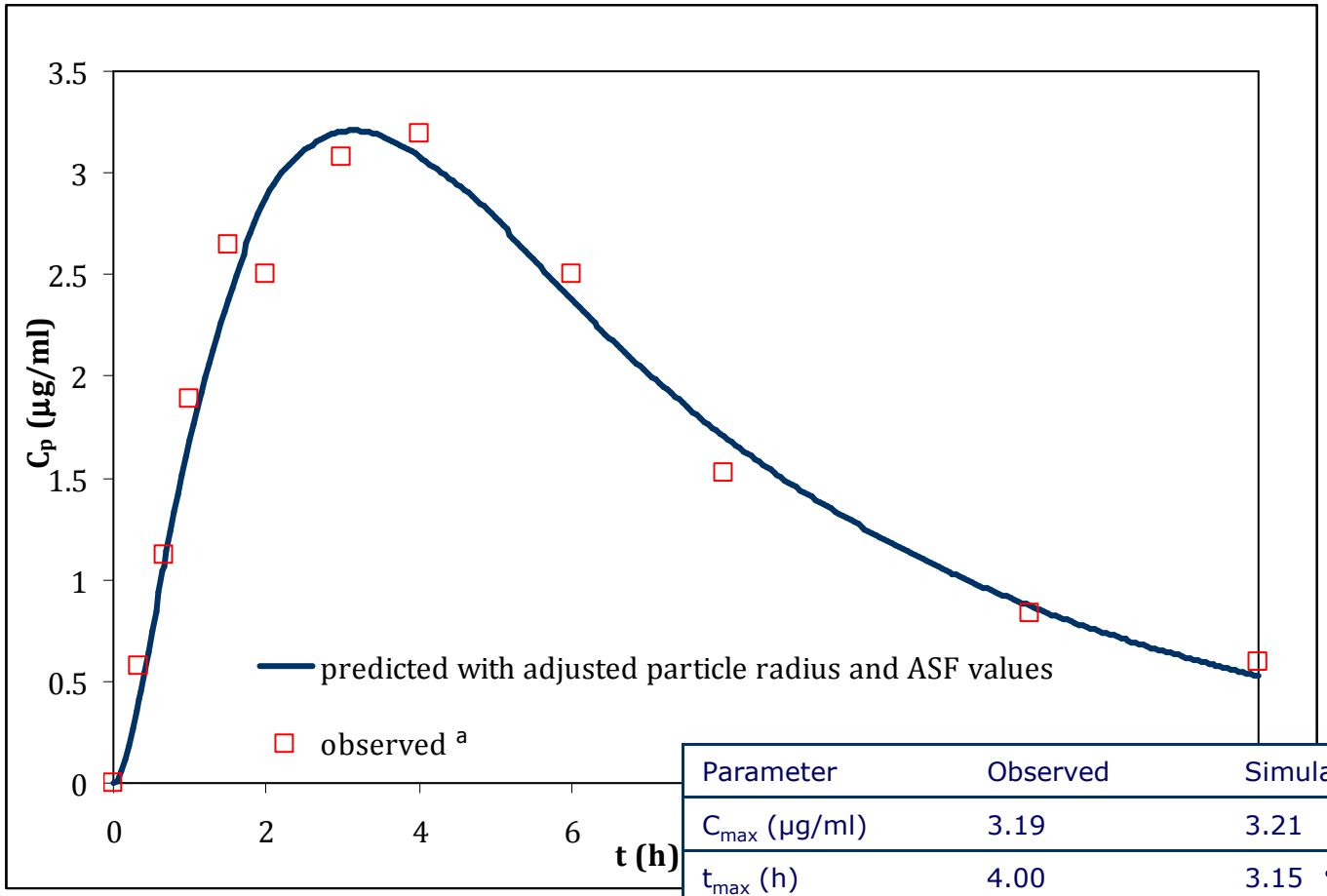
IR tablet



[a] Jovanovic D et al. Vojnosanit Pregl. 2005;62(12):887–93.

Model 1: Optimization...

IR tablet



reported t_{max}: 1-4 h [a,b]

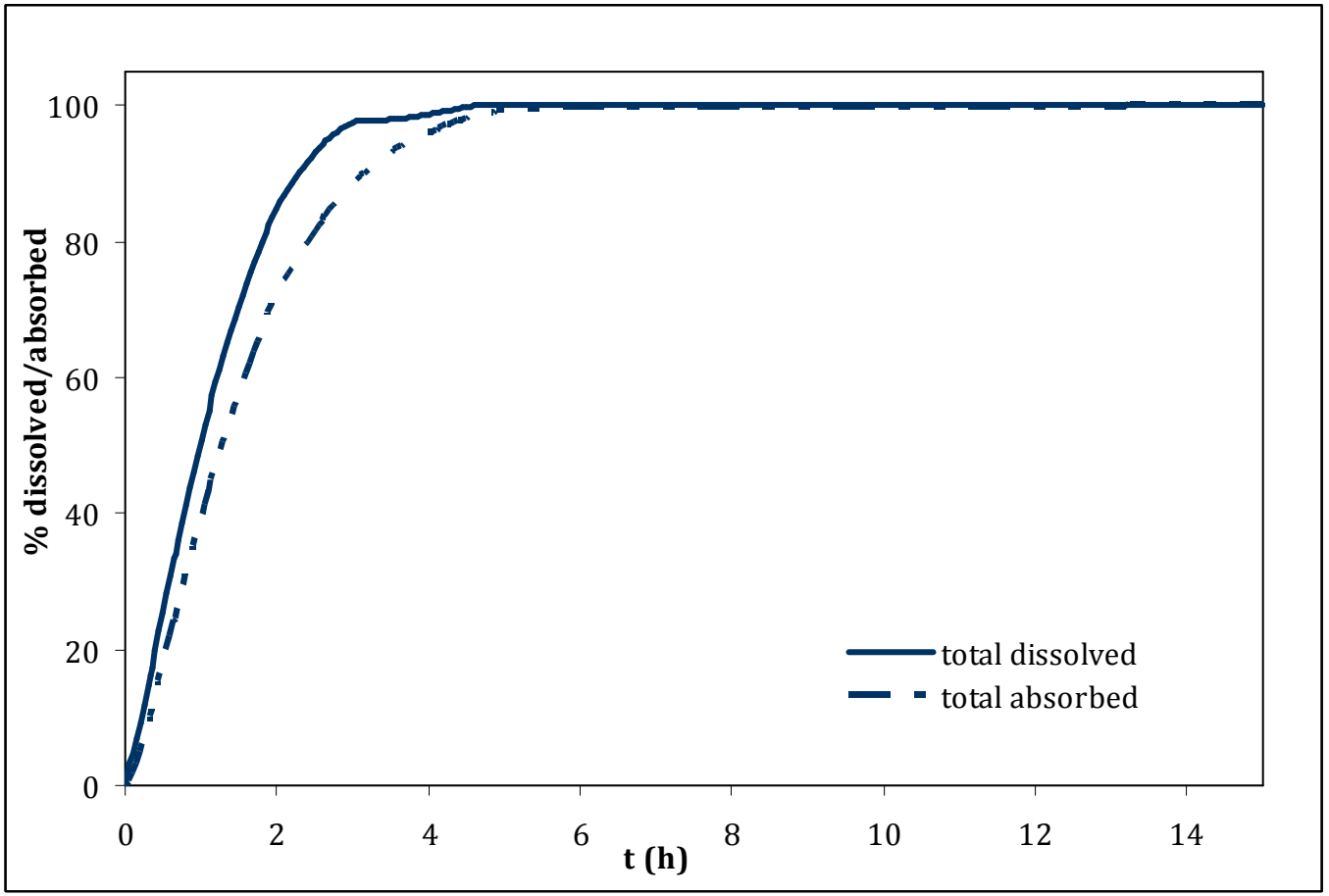
Parameter	Observed	Simulated	PE (%)
C_{max} (µg/ml)	3.19	3.21	-0.63
t_{max} (h)	4.00	3.15	21.25
$AUC_{0\rightarrow t}$ (µg h/mL)	25.78	25.96	-0.70
$AUC_{0\rightarrow\infty}$ (µg h/mL)	30.96	29.10	6.01

[a] Jovanovic D et al. Vojnosanit Pregl. 2005;62(12):887–93.

[b] Rainsford KD et al. Curr Med Res Opin. 2006;22(6):1161–70.

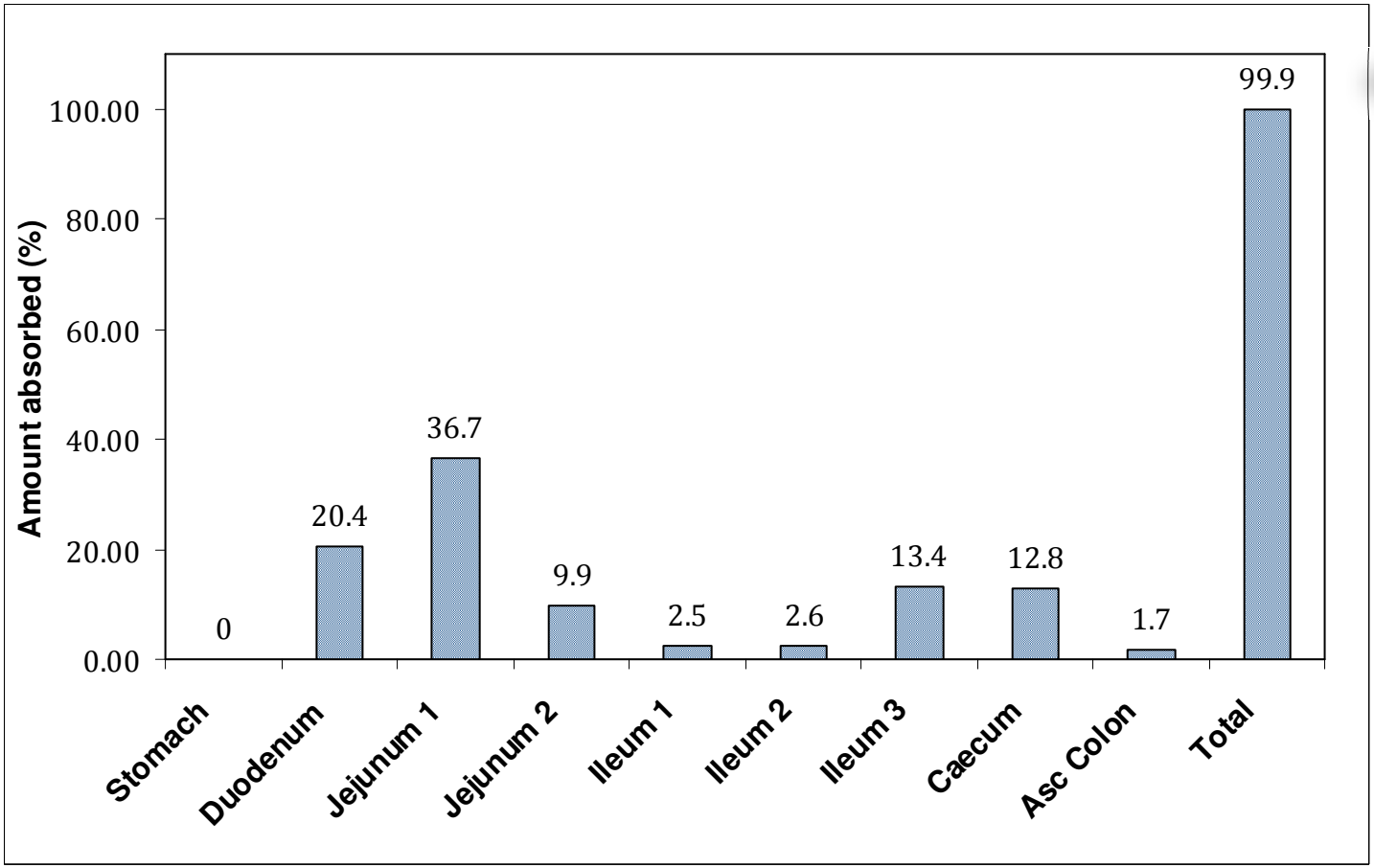
Model 1: Predicted NIM Dissolution and Absorption Profiles

IR tablet



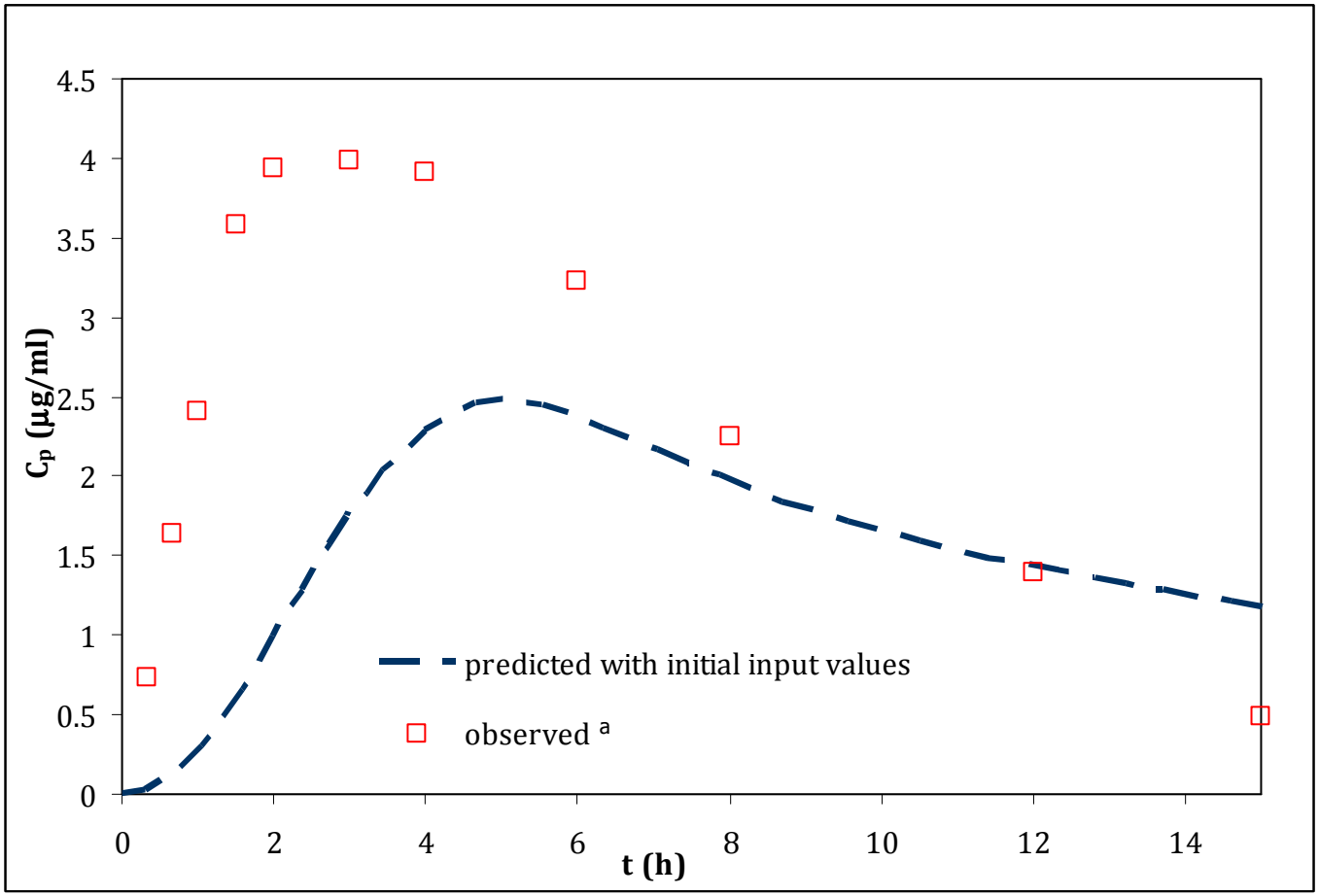
Model 1: Compartmental Absorption of NIM

IR tablet



IR suspension

Model 2: Initial Simulation Results...



[a] Jovanovic D et al. Vojnosanit Pregl. 2005;62(12):887–93.

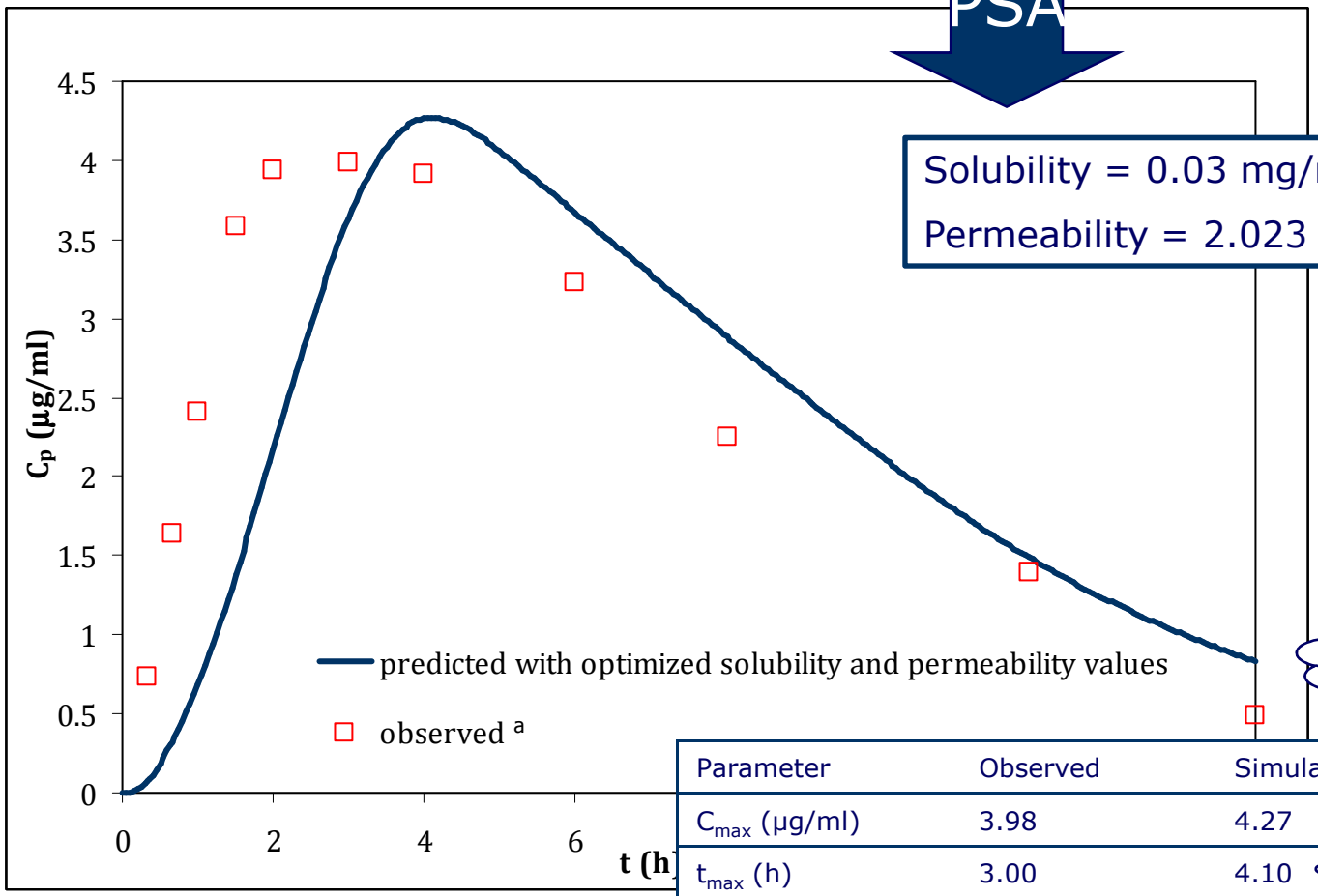
Model 2: Optimization...

IR suspension

PSA

Solubility = 0.03 mg/ml

Permeability = 2.023 x 10^{-4} cm/s



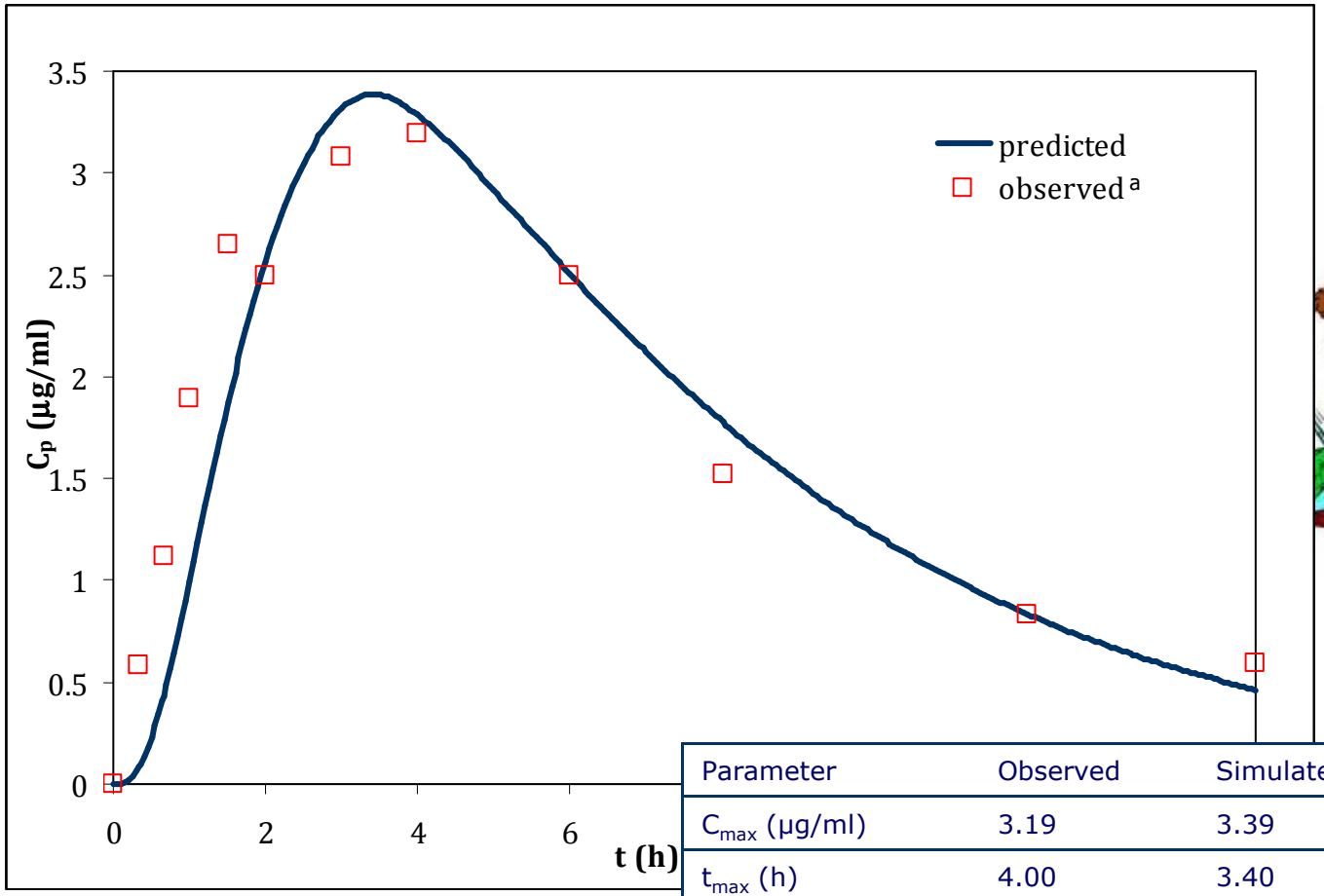
individual t_{max}: 1.5-6 h [a]

Parameter	Observed	Simulated	PE (%)
C_{max} (µg/ml)	3.98	4.27	-7.18
t_{max} (h)	3.00	4.10	-36.67
$AUC_{0\rightarrow t}$ (µg h/mL)	35.23	35.68	-1.30
$AUC_{0\rightarrow\infty}$ (µg h/mL)	36.61	39.60	-8.17

[a] Jovanovic D et al. Vojnosanit Pregl. 2005;62(12):887–93.

Model 2: Validation...

IR tablet



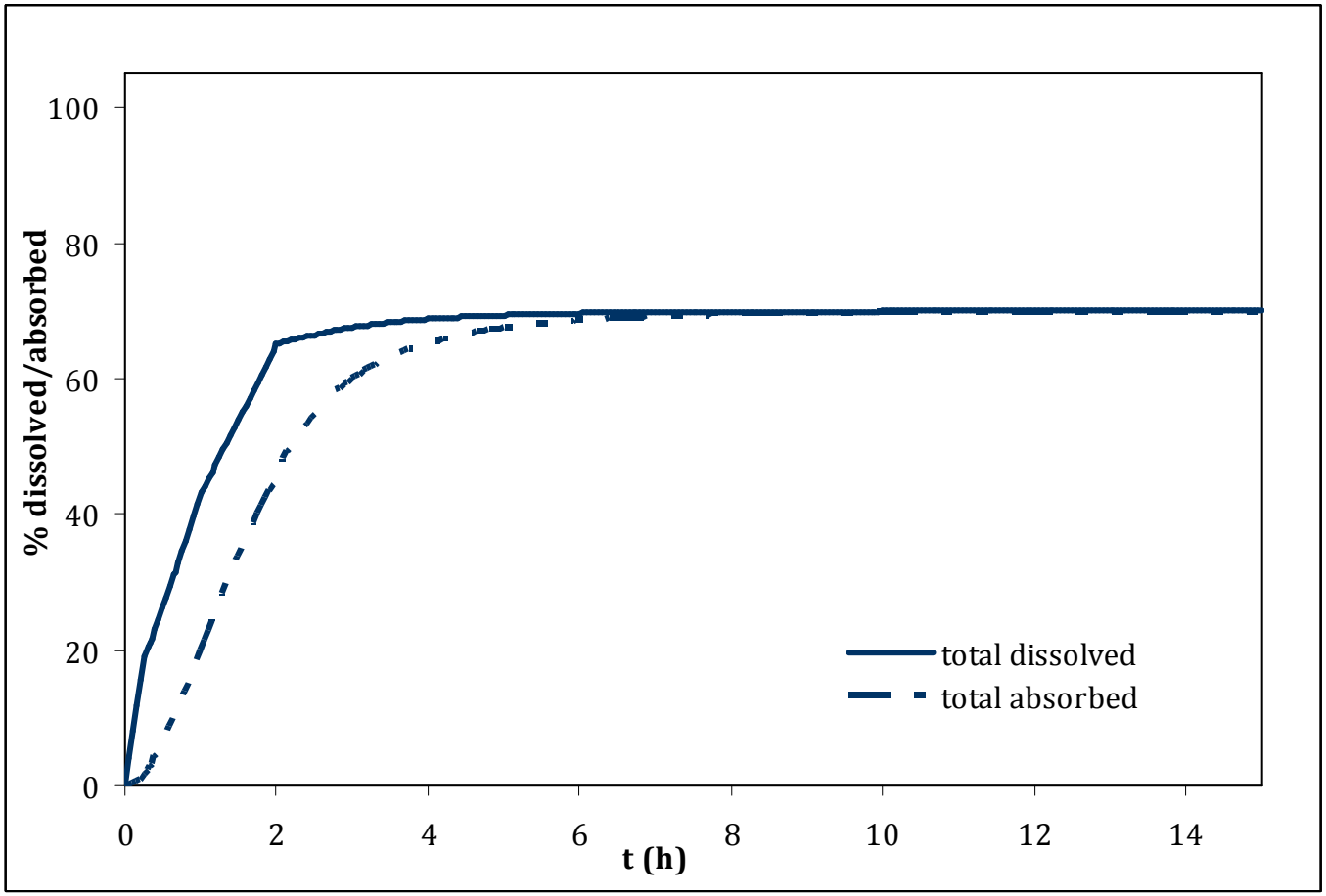
reported t_{max}: 1-4 h [a,b]

Parameter	Observed	Simulated	PE (%)
C_{max} (µg/ml)	3.19	3.39	-6.16
t_{max} (h)	4.00	3.40	15.00
$AUC_{0\rightarrow t}$ (µg h/mL)	25.78	25.69	0.35
$AUC_{0\rightarrow\infty}$ (µg h/mL)	30.96	27.92	9.82

[a] Jovanovic D et al. Vojnosanit Pregl. 2005;62(12):887–93.

[b] Rainsford KD et al. Curr Med Res Opin. 2006;22(6):1161–70.

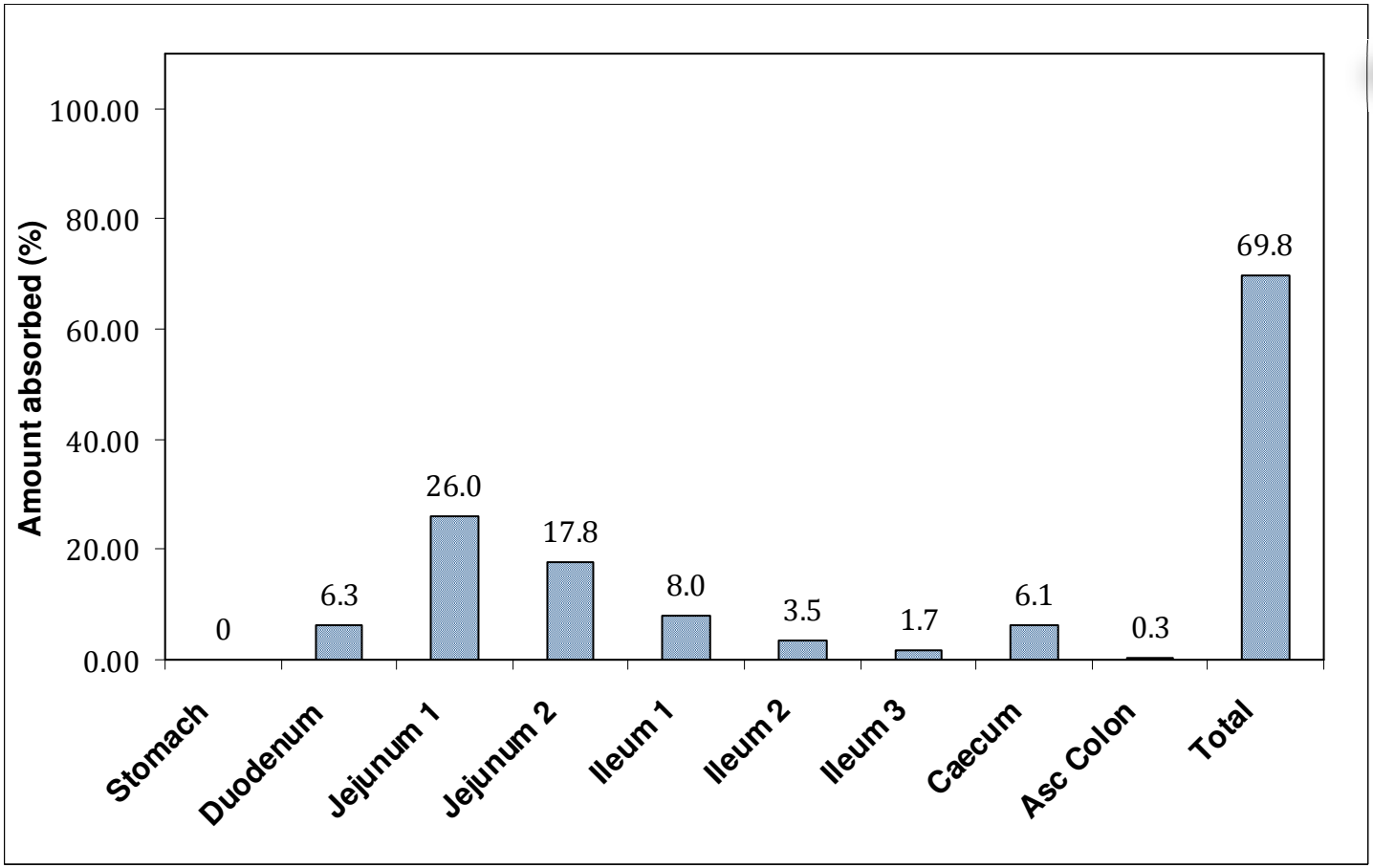
Model 2: Predicted NIM Dissolution and Absorption Profiles



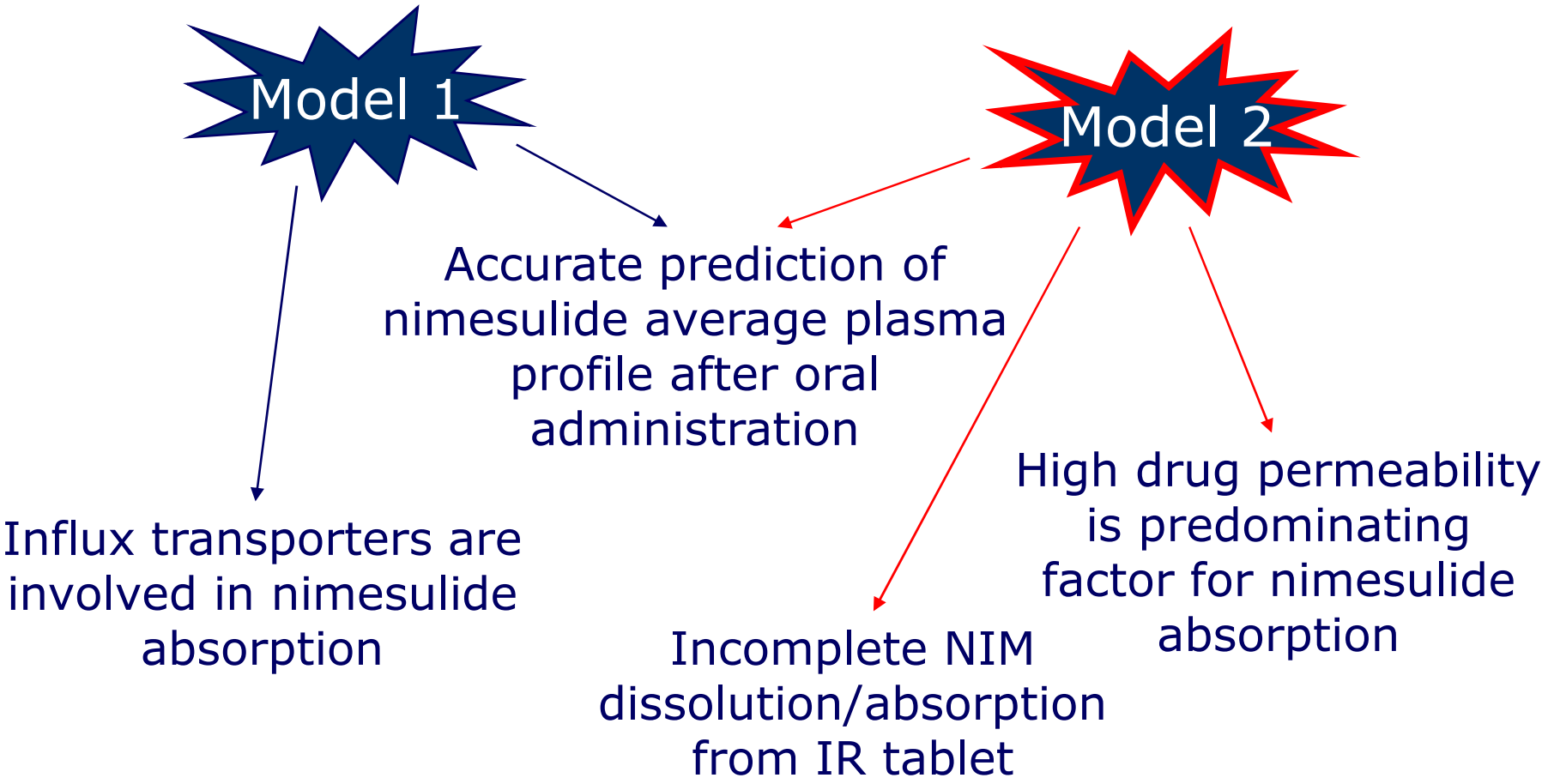
IR tablet

Model 2: Compartmental Absorption of NIM

IR tablet



Model Considerations



Conclusions

- Gastrointestinal simulation technology can be used for evaluation and prediction of oral drug absorption
- In order to obtain meaningful *in silico* modeling, the necessary input data have to be carefully selected and/or experimentally verified
- PSA is a valuable tool for identification of critical parameters affecting the rate and extent of drug absorption