M1330-05-036

HTPK: Conducting PK modeling and simulations at high speed

Robert Fraczkiewicz, David Miller, Marvin Waldman, and Robert D. Clark

Simulations Plus, Inc. 42505 10th Street West, Lancaster, CA 93534, USA

CONTACT INFORMATION: robert@simulations-plus.com

aaps PharmSci 360 ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

In silico pharmacokinetic (PK) simulations are now routinely incorporated into drug development workflows, especially in the later stages. Such simulations can provide insight into the results of Phase I/II clinical trials, which is crucial to deciding when or if to progress a drug candidate. For example, the best way to identify reasons for the lack of in vivo drug efficacy is through full-scale physiologically-based PK (PBPK) studies. There is no fundamental reason, however, not to use PK simulations in drug discovery. Practical arguments against doing so were computational cost and availability of appropriate input parameters. We present and test a new method that addresses these problems.

OBJECTIVE

This study is a comparison of predicted percent absorbed and percent bioavailable between the high throughput PK (HTPK) simulation module of ADMET Predictor™ and the ACAT™ / compartmental PK predictions from GastroPlus™ and tests its performance.

METHODS

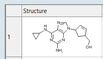
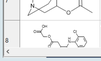
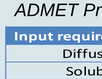
We have implemented a PK simulation capability (termed the HTPK Simulation Module) within ADMET Predictor [1] that runs compartmental PK simulations based on the Advanced Compartmental Absorption and Transit (ACAT™) model [2] while omitting some advanced capabilities (e.g., accounting for active transport). Special attention was paid to high computational performance. Inputs to the simulation are automatically generated from predictive ADMET or provided as experimental values, should those be available. In principle, only molecular structures are needed to run simulations.

RESULTS

HTPK calculation of fraction absorbed and fraction bioavailable in human after 24 h, at three different IR doses (1 mg, 10 mg, 100 mg) for each of the 2284 drugs extracted from the World Drug Index.

Platform	Processing time for 2284 drugs
Laptop A [3]	3.9 min (~0.1 s/drug)
Laptop B [4]	2.5 min (~0.06 s/drug)

*Table of results for the first 8 drugs of the 2284 set mentioned above. %Fa_hum = fraction absorbed in human, %Fb_hum = fraction bioavailable, Cmax_hum = maximal attained plasma concentration in ng/mL, Tmax_hum = time to reach Cmax in h, AUC_hum = area under the $C_p(t)$ curve in ng*h/mL. Numerical suffixes indicate dose in mg.*

	Structure	Identifier	%Fa_hum-1.0	%Fb_hum-1.0	Cmax_hum-1.0	Tmax_hum-1.0	AUC_hum-1.0	%Fa_hum-10.0	%Fb_hum-10.0	Cmax_hum-10.0	Tmax_hum-10.0	AUC_hum-10.0	%Fa_hum-100.0	%Fb_hum-100.0	Cmax_hum-100.0	Tmax_hum-100.0	AUC
1		ABACAVIR	99.420	90.850	6.040	2.940	75.170	99.440	90.870	60.420	2.940	751.680	99.460	90.890	604.390	2.940	
2		ACAMPROSATE_	92.180	79.700	16.920	1.630	52.490	92.120	79.650	169.140	1.630	524.570	92.190	79.720	1692.610	1.630	
3		ACARBOSE	1.430	0.830	0.055	1.470	0.550	1.430	0.840	0.550	1.470	5.470	1.430	0.840	5.460	1.470	
4		ACEBUTOLOL	83.160	62.290	3.010	3.090	27.610	83.130	62.270	30.050	3.090	276.010	83.200	62.340	300.670	3.090	
5		ACECAINIDE_A...	87.730	62.050	3.590	2.530	23.410	87.720	62.060	35.880	2.530	234.090	87.730	62.060	358.920	2.530	
6		ACECARBROM	99.920	73.340	7.890	1.460	25.280	99.920	73.340	78.890	1.460	252.810	99.920	73.340	790.210	1.470	
7		ACECLIDINE	97.610	84.400	5.090	1.880	40.490	97.620	84.410	50.890	1.880	404.900	97.630	84.420	508.960	1.880	
8		ACECLOFENAC	99.970	97.050	52.770	1.780	497.840	99.970	97.050	527.750	1.780	4978.510	99.970	97.040	5277.230	1.780	

Required inputs and corresponding ADMET Predictor models

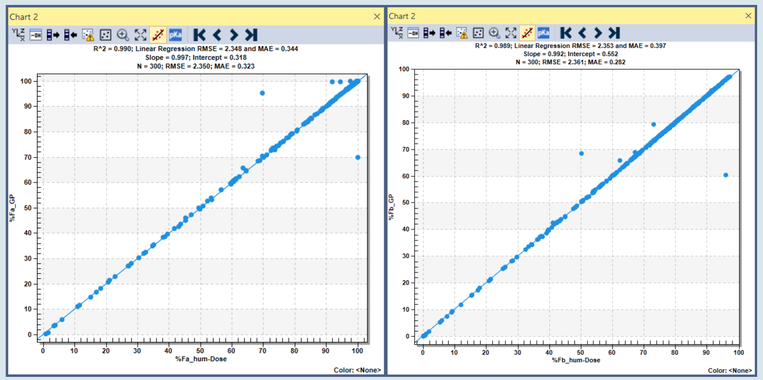
Input required for %Fa and %Fb	Model
Diffusivity in water	DiffCoef
Solubility in water	S+Sw
Salt solubility factor	SolFactor
Solubility in fasted intestinal fluid	S+FaSSIF
Solubility in fed intestinal fluid	S+FeSSIF
pKa	S+pKa
Human jejunal permeability	S+Peff
log P	S+logP
Volume of distribution	Vd
Percent unbound in plasma	hum_fup%
Microsomal fraction unbound	S+fumic
Metabolic clearance	CYP_HLM_CLint
Blood to plasma ratio	RBP
Precipitation time	<user input>
Dose	<user input>
Dose volume	<user input>
Particle radius	<user input>
Body weight	<user input>

Outputs generated by fraction absorbed / bioavailable and optimal dose models

Outputs generated by the %Fa/%Fb model
Fraction absorbed
Fraction bioavailable
Cp(t) = plasma concentration vs. time profile
C_max = maximum plasma concentration
t_max = time of peak plasma concentration
AUC = area under the Cp(t) curve
Sensitivity to permeability and solubility
Mechanistic estimation of the volume of distribution

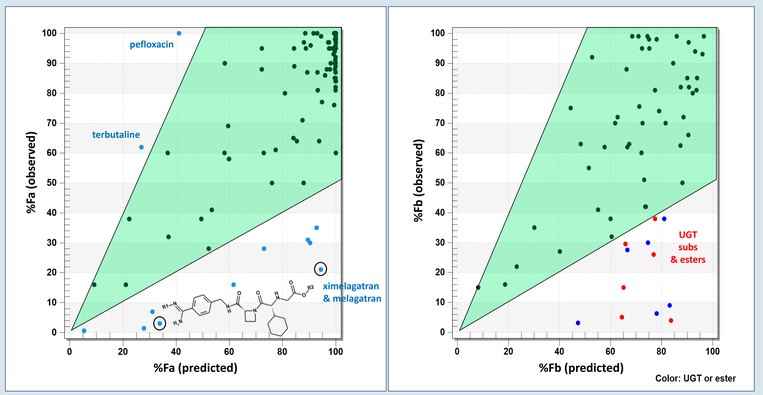
Outputs generated by the OptDose model
Optimal dose to reach desired plasma concentration at steady state

Comparison of HTPK simulation results (%Fa, left chart, and %Fb, right chart, all at 10 mg dose) vs. compartmental ACAT results obtained in GastroPlus [5] for a subset of 300 representative drugs extracted from the World Drug Index.



HTPK vs. experiment: predicted and observed human fraction absorbed for 115 passively-absorbed compounds published by Zhao et al. [6] 90% predicted were within 2-fold of the reported value, while 83% predicted were within 1.5-fold. There is some indirect evidence that pefloxacin and terbutaline are influx transporter substrates.

HTPK vs. experiment: predicted and observed human fraction bioavailable for 62 compounds metabolized primarily by hepatic CYPs. [7] 81% predicted were within 2-fold of the reported value, while 68% predicted were within 1.5-fold. Some outliers are determined to be P_{gp} and/or UGT substrates.



CONCLUSION

HTPK Simulation Module simulations can be expected to match experimental results as well as ACAT plus central compartmental analysis in GastroPlus does. The new HTPK Simulation Module in ADMET Predictor provides a high-throughput pharmacokinetic tool for addressing likely absorption and bioavailability problems early in drug discovery. It can quickly estimate bioavailability potential of thousands of analogs generated in silico, e.g., via combinatorial explosion, thereby saving both time and effort.

In summary, it is simple enough to be fast, yet complicated enough to get the job done.

REFERENCES

[1] ADMET Predictor™ v9.0 is distributed by Simulations Plus, Inc. (http://www.simulations-plus.com).

[2] Agoram, B.; Woltosz, W. S.; Bolger, M. B. “Predicting the impact of physiological and biochemical processes on oral drug bioavailability.” Adv. Drug. Deliv. Rev. **2001**, 50 Suppl 1, S41-67.

[3] DELL XPS with Intel® Core™ i7-3537U CPU 2.5 GHz, 8 GB RAM, 64-bit, running Windows 7.

[4] ASUS R.O.G. with Intel® Core™ i7-7700HQ CPU 2.8 GHz, 16 GB RAM, 64-bit, running Windows 10.

[5] GastroPlus™ v9.6 is distributed by Simulations Plus, Inc. (http://www.simulations-plus.com).

[6] Zhao et al. J. Pharm. Sci., **2001**, 90: 749.

[7] Toshimoto et al. Drug Metab. Dispos. **2014**, 42:1811.

SimulationsPlus

SCIENCE + SOFTWARE = SUCCESS