W5030

Application of the 'MechPeff' Model to Predict Passive Regional Effective Intestinal Permeability in Rat Using Drug Physicochemical Parameters as Inputs

D. Pade, M. Jamei, D.B. Turner

Simcyp Limited (a Certara Company), Sheffield, UK **(devendra.pade@certara.com)**

Introduction:

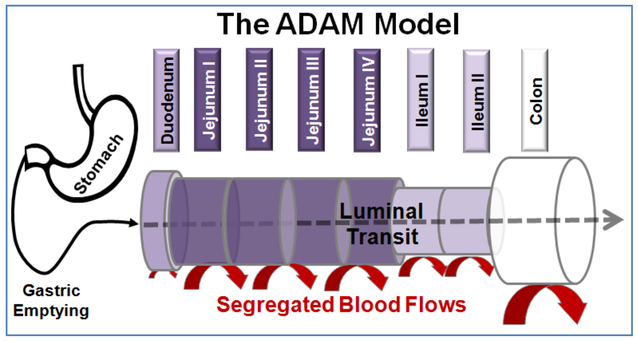
It is well known that prediction of oral bioavailability (F) using interspecies extrapolation is questionable **[1]**. Intestinal permeability (P_{eff}) of a drug is a key factor contributing to the fraction of drug absorbed into the enterocytes (fa) and thus overall F. Prediction of human intestinal permeability based on single pass intestinal perfusion (SPIP) experiments in rats and humans is known to show significant correlations **[2-4]**. Bottom-up mechanistic prediction of passive intestinal permeability in Sprague-Dawley rat can provide a high through-put tool for permeability screening of drug discovery candidates, thus impacting the implementation of the 3R's.

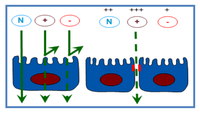
Specific Aim:

To evaluate the performance of a mechanistic permeability model ('**MechPeff**') to predict the passive permeability ($P_{eff,rat}$) in different intestinal regions of the Sprague Dawley rat against experimental SPIP values.

Methods:

The '**MechPeff**' model within the Advanced Dissolution, Absorption and Metabolism (ADAM) model of Simcyp Rat (v14) was used to predict the jejunal and ileal $P_{eff,rat}$ (n=45) for various drugs and compared to *in vivo* measurements determined using the Single Pass Intestinal Perfusion (SPIP) technique **[2-4]**. The 'MechPeff' model is largely similar to that described in **[5]** and explicitly considers passive transcellular and paracellular permeability, GI morphology, unstirred boundary layer (UBL) thickness and pH and impact of bile salt micelle partitioning on drug free fraction. The model requires as a minimum the following drug-specific inputs: intrinsic transcellular permeability ($P_{trans,0}$) (can be predicted from $P_{o:w}$ or $P_{PAMPA,0}$), pKa and type, and MWt.





Transcellular and Paracellular Permeability
pH Partition Hypothesis
Molecule-Pore Size

References:

1. Musther H. 2014, Eur J Pharm Sci.; 16; 57:280-91; **2.** Zakeri-Milani P. 2007, J Pharm Pharm Sci.;10 (3): 368-79; **3.** Salphati L. 2001, J Pharm Pharmacol.; 53 (7): 1007-13; **4.** Kim JS. 2006, Mol Pharm. 2006; 3 (6): 686-94; **5.** Pade D. 2014, Poster W5106 at AAPS 2014 Annual Meeting, San Diego, USA.

Drug Parameters and Rat Jejunal/Ileal $P_{eff,rat}$ Values

Drug	MWt.	log$P_{O:W}$	$P_{trans,0}$ x 10^{-6} cm/s	Jejunal/Ileal P_{eff} x 10^{-4} cm/s			
				Observed		Predicted using	
				P_{eff}	± SD	log$P_{o:w}$	$P_{trans,0}$
Cephalexin Jejunum	347	-0.81	0.9	0.75	0.33	0.019	0.019
L-leucine Jejunum	131	-1.77	3.5	3.88	0.00	0.223	0.223
Cefalexin Ileum	347	-0.81	0.9	0.260	0.060	0.011	0.011
Enalapril Jejunum	376	0.07	NA	0.81	0.000	0.005	NA
Enalaprilat Jejunum	348	-1.25	2.8	0.06	0.000	0.006	0.006
Fluvastatin Jejunum	411	4.17	46774	0.60	0.000	0.674	3.566
Furosemide Jejunum	331	2.56	316	0.17	0.15	0.051	0.057
Ibuprofen Jejunum	206	4.13	295121	2.00	0.22	0.690	6.497
Ketoprofen Jejunum	254	3.16	58884	1.04	0.36	0.226	3.518
Losartan Jejunum	423	3.09	109.6	0.86	0.00	0.023	0.007
Naproxen Jejunum	230	3.24	112201.8	0.65	0.76	0.313	4.948
Piroxicam Jejunum	331	1.98	9772	1.705	1.294	0.800	4.622
Furosemide Ileum	331	2.56	316	0.164	0.037	0.031	0.035
Ketoprofen Ileum	254	3.16	58884	1.090	0.720	0.140	1.396
Naproxen Ileum	230	3.24	112202	1.670	0.820	0.197	1.645
Sulfasalazine Ileum	398	3.61	2188	0.060	0.030	0.014	0.037
Atenolol Jejunum	266	0.22	46	0.07	0.06	1.498	1.860
Caffeine Jejunum	324	-0.07	72	0.50	0.06	1.239	2.213
Cimetidine Jejunum	252	0.48	0.9	0.29	0.27	1.012	0.150
Metoprolol Jejunum	267	1.95	14125	0.25	0.07	0.161	1.500
Propranolol Jejunum	259	3.48	28840	0.581	0.176	0.295	2.174
Quinidine Jejunum	324	3.44	490	0.370	0.000	0.796	0.682
Ranitidine Jejunum	314	1.28	5.4	0.147	0.104	0.358	0.100
Terbutaline Jejunum	225	-0.08	5.9	0.050	0.000	0.192	0.178
Valacyclovir Jejunum	324	-0.30	NA	0.370	0.000	0.306	NA
Verapamil Jejunum	455	4.33	6606.9	0.650	0.000	0.662	1.459
Vincristine Jejunum	824	3.49	2.9	1.575	0.000	1.519	0.036
Aciclovir Ileum	225	-1.77	3.7	0.070	0.020	0.108	0.108
Atenolol Ileum	266	0.22	45.7	0.180	0.090	0.853	0.985
Metoprolol Ileum	267	1.95	14125.4	0.590	0.130	0.099	0.853
Nadolol Ileum	309	0.85	33.9	0.043	0.007	0.053	0.052
Propranolol Ileum	259	3.48	28840.3	0.690	0.042	0.185	1.087
Terbutaline Ileum	225	-0.08	5.9	0.120	0.090	0.119	0.110
Amoxicillin Jejunum	365	-1.71	2.0	0.12	NA	0.490	0.269
Antipyrine Jejunum	188	0.56	89.1	0.78	0.02	1.921	2.795
Carbamazepine Jejunum	236	2.45	204.2	1.21	0.83	4.012	3.727
Hydrochlorothiazide Jejunum	298	-0.03	0.5	0.07	0.07	1.289	0.106
Levodopa Jejunum	197	-2.47	0.8	3.36	0.00	0.367	0.201
Paracetamol Jejunum	151	0.34	45.7	0.26	0.01	1.823	2.135
Phenylalanine Jejunum	165	-1.38	23.4	2.32	0.00	0.735	1.484
α-Methyldopa Jejunum	211	-1.70	NA	0.123	0.151	0.566	NA
Antipyrine Ileum	188	0.56	89.1	0.730	0.020	1.064	1.336
Dexamethasone Ileum	392	1.74	22.4	1.570	0.210	1.108	0.684
Digoxin Ileum	765	1.29	3.7	0.218	0.043	0.796	0.235
Hydrochlorothiazide Ileum	298	-0.03	0.5	0.070	0.030	0.755	0.065

NEUTRAL | ACIDIC | BASIC | AMPHOLYTIC

Results:

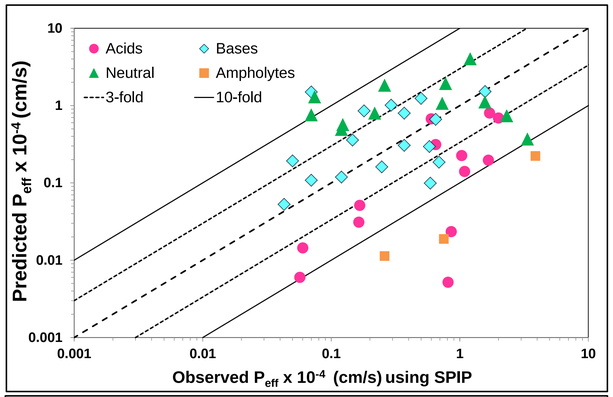


Fig. 1: Predicted vs. Observed Jejunum & Ileum $P_{eff,rat}$; $P_{O:W}$ as input

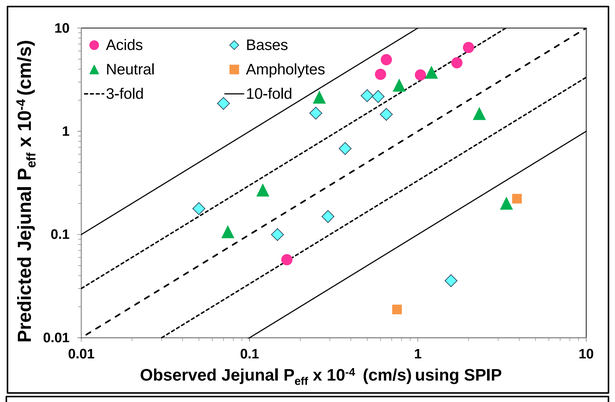


Fig. 2: Predicted vs. Observed Jejunal $P_{eff,rat}$; Exp $P_{trans,0}$ as input

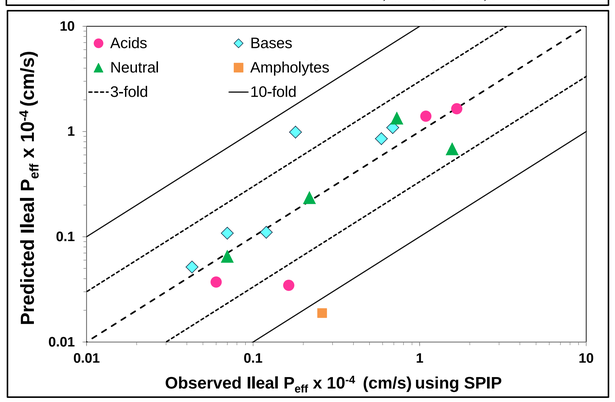


Fig. 3: Predicted vs. Observed Ileal $P_{eff,rat}$; Exp. $P_{trans,0}$ as input

Conclusion:

The 'MechPeff' model is reasonably successful at predicting the passive jejunal & ileal intestinal permeability in Sprague Dawley rat. The predictions are in best agreement with experimental values when intrinsic transcellular permeability ($P_{trans,0}$) derived from modelling of *in vitro* cell line experiments is used as input to the model.