W5029

In Silico Prediction of Regional Passive Intestinal Permeability in Cynomolgus Monkey using 'MechPeff': A Mechanistic Model with Drug Physicochemical and In Vitro Parameters as Inputs

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Introduction:

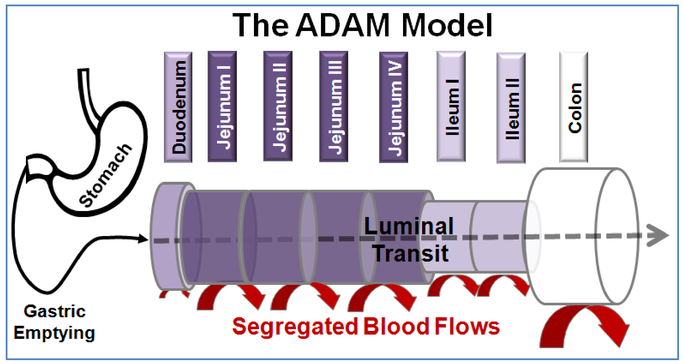
Passive drug permeability across the wall of the gastro-intestinal (GI) tract can significantly vary from one region to another due to structural and morphological differences. Unlike other common preclinical species, the cynomolgus monkey GI tract exhibits permanent folds known as the plicae circulares which are known to enhance the surface area for absorption leading to regional and species differences in drug permeability. Literature survey indicates that measurement of effective intestinal permeability ($P_{eff,monkey}$) in non-human primates (NHP) is rare. Hence mechanistic models based upon *system* knowledge can be used to predict the passive $P_{eff,monkey}$ in the different regions of the cynomolgus GI tract.

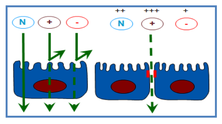
Specific Aim:

- To evaluate the performance of a Mechanistic Passive Permeability prediction model ('**MechPeff**') to predict the jejunal $P_{eff,monkey}$ for 8 drugs in the cynomolgus monkey.

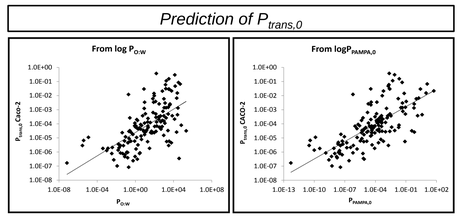
Methods:

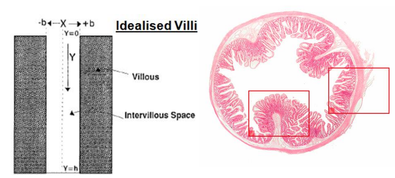
The '**MechPeff**' model within the Advanced Dissolution, Absorption and Metabolism (ADAM) model of Simcyp Monkey (v15) was used to predict jejunal $P_{eff,monkey}$ for 8 compounds and compared to in vivo measurements determined using the Single Pass Intestinal Perfusion (SPIP) technique **[1,2]**. The 'MechPeff' model is largely similar to that described in **[3]** 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.





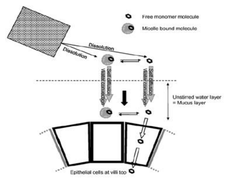
Transcellular and Paracellular Permeability pH Partition Hypothesis Molecule-Pore Size



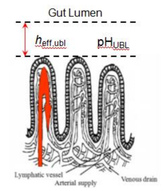


Villous Morphology (VE Scalar)

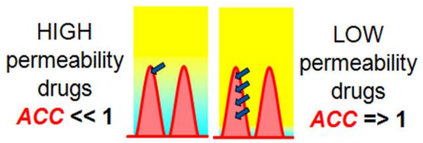
Plicae Circulares Fold Expansion



Bile Salt Micelle Partitioning [3]



UBL pH & Thickness



Villous Accessible Surface Area

Drug Parameters and Cynomolgus Jejunal $P_{eff,monkey}$ Values

Drug	MWt.	log$P_{O:W}$	Caco-2 $P_{trans,0}$ x 10^{-6} cm/s	Obsd. Jejunal P_{eff} x 10^{-4} cm/s		Predicted Jejunal P_{eff} x 10^{-4} cm/s		
				P_{eff}	± SD	log$P_{o:w}$	log$P_{PAMPA,0}$	$P_{trans,0}$ Caco-2
Antipyrine	188	0.56	89	1.36	0.46	3.29	2.10	5.02
Atenolol	266	0.22	46	0.31	0.12	0.16	0.16	0.17
Acetaminophen	151	0.34	46	1.57	0.31	3.06	2.06	3.66
Piroxicam	331	1.98	9772	2.24	0.56	1.33	1.47	10.15
Propranolol	259	3.48	28840	0.955	0.4	0.39	1.76	4.76
Verapamil	454	4.33	6607	0.93	0.64	1.09	2.72	3.08
Midazolam	325	3.53	363	6.84	0.11	9.70	8.56	8.26
Nadolol	309	0.71	34	0.28	0.02	0.11	0.11	0.11

Compound type classification is based upon predominant species at pH 6.5 (the model itself accounts for the relative proportions of ion species according to pH and pKa(s))

NEUTRAL | ACIDIC | BASIC

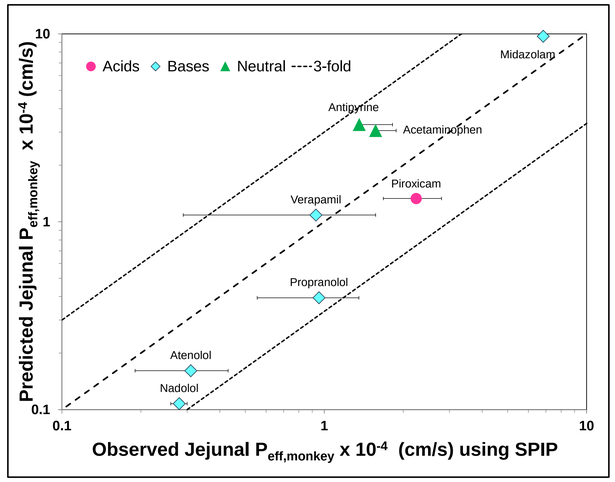


Fig. 1: Predicted vs. Observed Jejunal $P_{eff,monkey}$; $logP_{O:W}$ as input

Results:

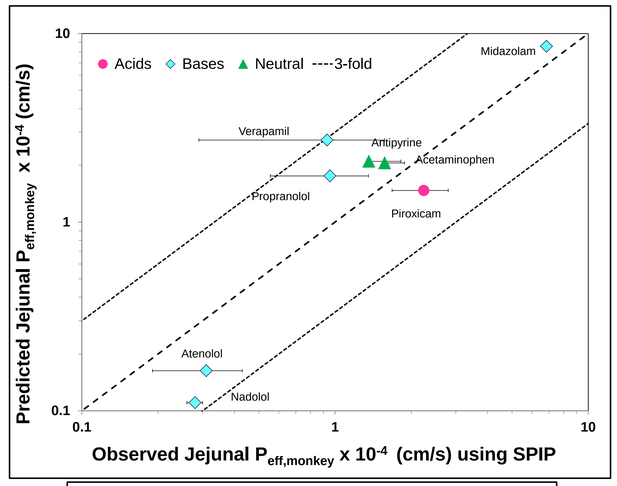


Fig. 2: Predicted vs. Observed Jejunal $P_{eff,monkey}$; $logP_{PAMPA,0}$ as input

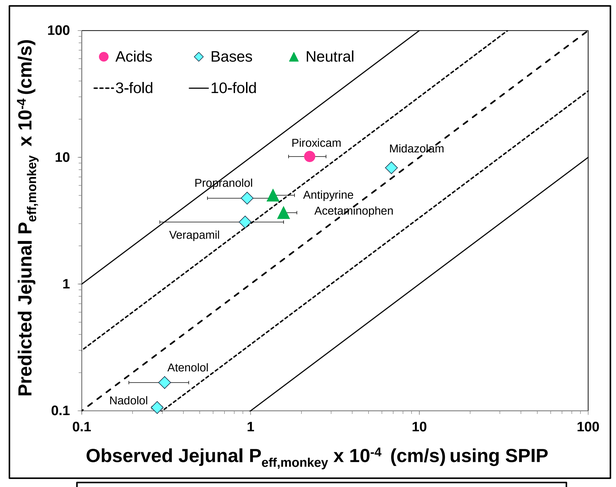


Fig. 3: Predicted vs. Observed Jejunal $P_{eff,monkey}$; $P_{trans,0}$ as input

For the data set of 8 drugs, which included 5 bases, 2 neutrals and 1 acid, (Fig. 1 & Fig. 2) Jejunal $P_{eff,monkey}$ predictions (using log$P_{O:W}$ & log$P_{PAMPA,0}$ as input) were within 3-fold of the observed values. Predicted $P_{eff,monkey}$ values using intrinsic transcellular permeability ($P_{trans,0}$ Caco-2, Fig. 3) as input were within 3 fold for 4 drugs and within 10 fold for remaining 4 drugs.

Conclusion:

The 'MechPeff' model is reasonably successful at predicting the passive jejunal intestinal permeability in the cynomolgus monkey. The predictions are in best agreement with experimental values when $logP_{O:W}$ or $logP_{PAMPA,0}$ are used as input to the model. Further experimental data are required to test the performance for other GI regions.

Acknowledgement: Dr Kiyohiko Sugano for extremely helpful advice during model development.

References:
1. Sakuda S. 2006, Xenobiotica; 36: 331; **2.** Takahashi M. 2010, *Biol Pharm Bull*; 33:111;
3. Pade D. 2014, Poster W5106 at AAPS 2014 Annual Meeting, San Diego, USA.