W5106

A Mechanistic Framework for the *In Silico* Prediction of Regional Passive Gut Wall Permeability and it's Inter-individual Variability in Humans

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Introduction:

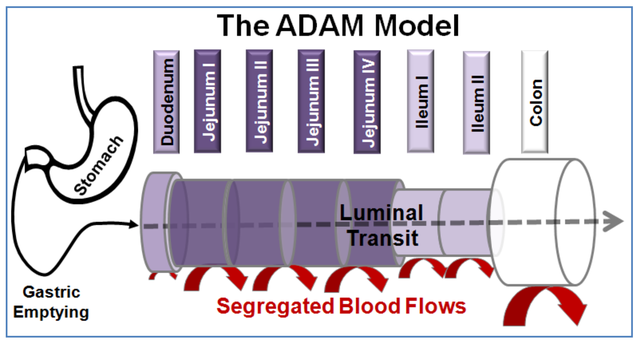
Human intestinal permeation is a complex multifactorial process dependent upon the interplay of the complex anatomy and physiology of the intestine (the "*system*") and the API (or formulation) physico-chemistry. Experimental determination of human intestinal effective permeability ($P_{eff,human}$) using the gold standard Loc-i-Gut method **[1]** is expensive, time consuming and largely restricted to the jejunum. Mechanistic models based upon *system* knowledge can be used to predict P_{eff} in both the jejunum and other intestinal regions. Also, a population-based approach incorporates where known the inter-individual variability (IIV) of the *system* components (*e.g.*, villous dimensions) enabling the IIV of regional P_{eff} to be predicted rather than only an "average" value for a representative individual.

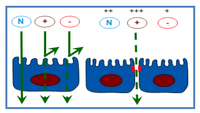
Specific Aims:

- To evaluate the performance of a Mechanistic Passive Permeability prediction model ('**MechPeff**') to predict human jejunal P_{eff} (hereafter P_{eff}).
- To evaluate where possible the extent of predicted IIV of P_{eff} based upon knowledge of the IIV of various *system* parameters.

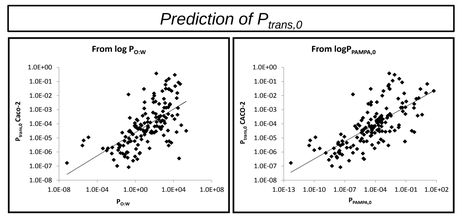
Methods:

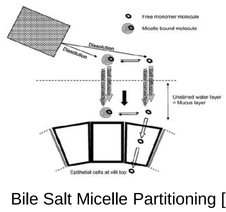
The '**MechPeff**' model within the Advanced Dissolution, Absorption and Metabolism (ADAM) model of Simcyp v14 was used to predict jejunal P_{eff} for 37 compounds and compared to Loc-i-Gut method **[2]** *in situ* values. The 'MechPeff' model is based upon the models of Sugano **[3]** and explicitly considers passive transcellular and paracellular permeability, gastrointestinal (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}), pKa and type, and MWt.



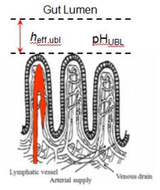


Transcellular and Paracellular Permeability
pH Partition Hypothesis
Molecule-Pore Size

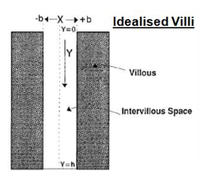


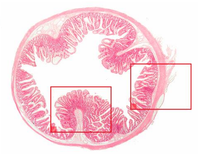


Bile Salt Micelle Partitioning [3]

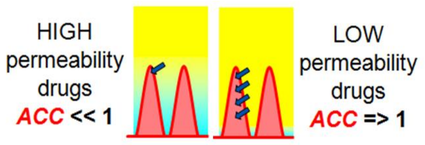


UBL pH & Thickness





Plicae Circulares
Fold Expansion



Villous Accessible Surface Area

Drug Parameters and Human Jejunal P_{eff} 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$P_{o:w}$	$P_{trans,0}$ Caco-2	±SD*
Acetaminophen	151.2	0.34	45.71	1.76$	0.43	3.06	3.66	0.81
α- Me - DOPA	211.2	-1.7	n/a	0.20	0.06	0.81	ND	ND
Amiloride	229.6	-0.26	17.78	1.63	0.51	0.23	0.23	0.06
Amoxicillin (Amox)	365.1	-1.71	2.00	0.34	0.11	0.71	0.36	0.09
Antipyrine (Antpy)	188.1	0.56	89.13	5.21	1.62	3.29	5.02	1.11
Atenolol (Atn)	266.3	0.22	45.71	0.20	0.20	0.16	0.17	0.05
Benserazide	257.1	-3.24	n/a	2.90	1.30	0.26	ND	ND
Carbamazepine (Cbz)	236.1	2.45	204.17	4.30	2.70	7.63	7.03	1.56
Cephalexin (Ceplx)	347.4	-0.81	0.93	1.56	0.00	0.02	0.02	0.01
Cimetidine (Cmt)	252.3	0.48	0.87	0.44	0.28	1.61	0.19	0.05
Cyclosporine A	1201.8	3.54	5.75	1.63	0.03	5.65	0.69	0.16
Desipramine	266.4	3.79	21379.62	4.45	0.07	0.23	1.38	0.32
Enalapril	376.2	0.07	n/a	1.57	0.00	0.01	ND	ND
Enalaprilat	348.4	-1.25	2.82	0.20	0.10	0.01	0.01	0.00
Fexofenadine (Fexo)	501.3	4.58	0.35	0.08	0.03	0.08	0.00	0.00
Fluvastatin (Fluv)	411.5	4.17	46773.51	2.38	1.85	1.04	6.88	1.54
Furosemide (Furs)	330.7	2.56	316.23	0.25	0.18	0.06	0.07	0.02
Griseofulvin	352.1	2.18	n/a	1.14	0.45	6.16	ND	ND
Hydrochlorothiazide (Hct)	297.7	-0.03	0.48	0.12	0.11	2.15	0.13	0.04
Inogatran	452.3	-0.6	n/a	0.03	0.03	1.42	ND	ND
Retinoic acid	300.4	6.3	n/a	0.99	0.00	4.83	ND	ND
Ketoprofen (Keto)	254.28	3.16	58884.37	8.45	0.07	0.06	2.39	0.55
Lisinopril (Lisn)	405.2	-2.42	2.09	0.33	0.00	0.01	0.01	0.00
L-Leucine	131.1	-1.77	3.55	6.20	2.93	0.93	0.81	0.20
Losartan (Losrt)	422.9	3.09	109.65	1.14	1.10	0.03	0.01	0.00
L-Phenylalanine (L-Phn)	165.1	-1.38	23.44	4.07	0.51	1.07	2.43	0.54
Metoprolol	267.4	1.95	14125.38	1.16	0.26	0.20	2.54	0.58
Naproxen	230.3	3.24	112201.85	8.96	0.97	0.32	8.69	1.95
Piroxicam	331.3	1.98	9772.37	7.06	0.64	1.25	9.04	2.01
Propranolol (Prpn)	259.3	3.48	28840.32	3.04	0.48	0.39	3.86	0.87
Ranitidine (Rnt)	314.4	1.25	5.37	0.37	0.14	0.48	0.12	0.03
Salicylic acid	138.1	2.19	371535.23	2.67	0.14	0.07	5.35	1.21
Sulphoraphane	177.0	1.68	n/a	18.70	12.60	5.93	ND	ND
Terbutaline (Tbt)	225.3	-0.08	5.89	0.30	0.30	0.25	0.23	0.06
Urea	60.1	-2.11	n/a	1.40	0.00	1.47	ND	ND
Valacyclovir	324.3	-0.3	n/a	1.66	0.00	0.41	ND	ND
Verapamil (Ver)	454.6	4.33	6606.93	6.70	2.90	1.03	2.54	0.58

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))

* SD from 100 simulated individuals. **$** Observed Jejunal P_{eff} value from Gramatte *et al.* (not Loc-i-Gut)

NEUTRAL | ACIDIC | BASIC | AMPHOLYTIC

Results:

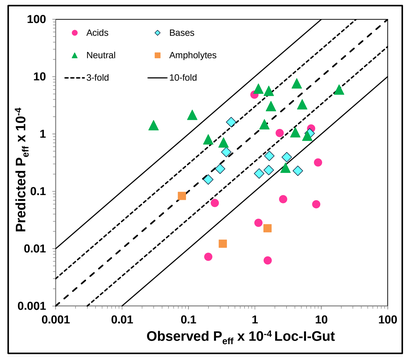


Fig. 1: Predicted vs. Observed Jejunal $P_{eff,human}$; $P_{O:W}$ as input

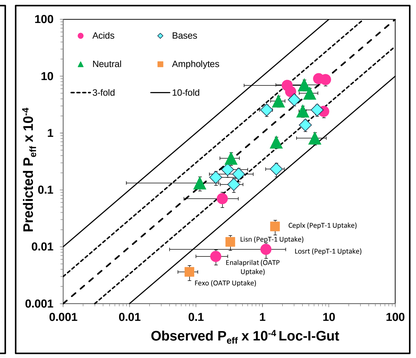
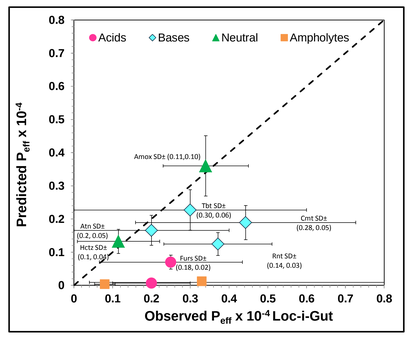
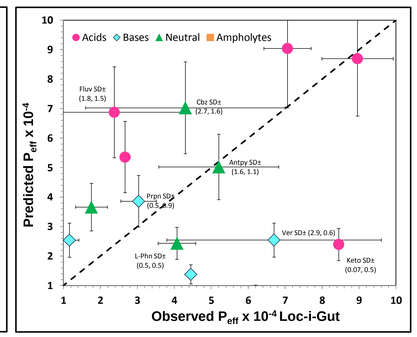


Fig. 2: Predicted vs. Observed Jejunal $P_{eff,human}$; exp. $P_{trans,0}$ as input





Figs. 3 & 4: Predicted (from exp. $P_{trans,0}$) vs. Observed Jejunal $P_{eff,human}$ with Inter-Individual Variability (IIV) indicated as SD values.

For 37 drugs (Fig. 1) predictions were: 10 or 25 within 3- and 10-fold respectively, and 12 beyond 10-fold of observed P_{eff} where $P_{trans,0}$ was predicted from $P_{o:w}$. Predictions improved significantly (Fig. 2) if using $P_{trans,0}$ derived from *in vitro* cell line studies (subset of 28 drugs) - 19 drugs were within 3-fold and 5 drugs beyond 10-fold (under-predicted) of observed P_{eff}; the latter are substrates for gut uptake transporters thus providing a plausible explanation for the under-prediction. For drugs with P_{eff} > 1 x 10^{-4} cm/s predicted and observed IIV of P_{eff} is comparable in most cases (Fig. 4). The observed IIV of P_{eff} is higher for the low permeability drugs and the model under-predicts this IIV.

Conclusion:

The 'MechPeff' model is reasonably successful at predicting the passive jejunal intestinal permeability along with its associated IIV. The predictions are in best agreement with experiment when the key input parameter $P_{trans,0}$ is derived from modelling of *in vitro* cell line studies.

References:
1. Lennernäs H. 1992, Pharm. Res. 9(10):1243; **2.** Avdeef A. 2012, Absorption and Drug Development, p 539-40; 2nd Edtn.; **3.** Sugano K. 2009, Int J Pharmaceut 373:55.

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