R6070

Prediction of Effective Regional Passive Intestinal Permeability in Mouse using 'MechPeff': A Mechanistic Model able to use only Drug Physicochemical Parameters as Inputs

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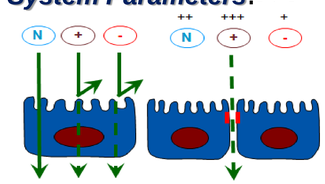
Introduction: The intestinal permeability of a drug is a composite function of passive permeability and active transport. Physiologically-Based Pharmacokinetic (PBPK) models help dissect these processes using a 'bottom-up' approach by combining species physiology (system parameters) with drug parameters. The following work combines detailed analysis of species gut physiology and morphology, readily available drug physicochemical parameters and a mechanistic algorithm to predict the passive intestinal permeability of a drug in mouse.

Purpose: PBPK modelling of drug disposition in the mouse is of particular relevance to intestinal transporter knock-out studies [1]. A prerequisite for modelling intestinal transporter-mediated permeability is knowledge of the passive component ($P_{eff,mouse}$). Experimental determination of $P_{eff,mouse}$ is difficult and rarely performed. To our knowledge models for the prediction of $P_{eff,mouse}$ have not been published. Herein we evaluate a mechanistic model ('MechPeff') to predict passive $P_{eff,mouse}$ in different intestinal regions. As a minimum the model requires as inputs only widely available physicochemical properties for the compound of interest.

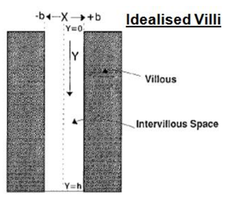
Methods: A mechanistic permeability ('MechPeff') model is incorporated in the Advanced Dissolution, Absorption and Metabolism model of the Simcyp Mouse Simulator (Version 12 Release 2).

System Parameters:[2,3]

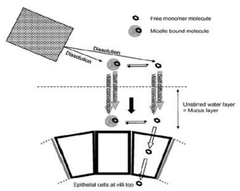


Transcellular Permeability pH Partition Hypothesis

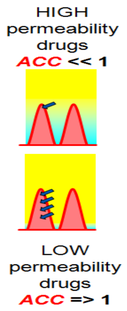
Paracellular Permeability Molecule-Pore Size



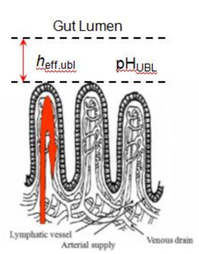
Villous Morphology (VE Scalar)



Bile Salt Micelle Partitioning



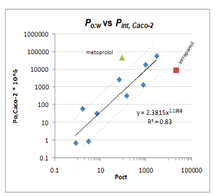
Villous Accessible Surface Area



UBL pH & Thickness

in vivo $P_{transcellular,intrinsic}$ = *in vitro* Caco- 2 $P_{transcellular,intrinsic}$

From $P_{o:w}$

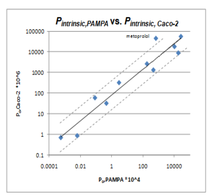


+/-5-fold

$P_{trans,Caco-2,int} = 2.381 \times 10^{-6} P_{oct}^{1.197}$

Model domain: $0 < \log P_{o:w} < 3.5$

From $P_{intrinsic,PAMPA}$



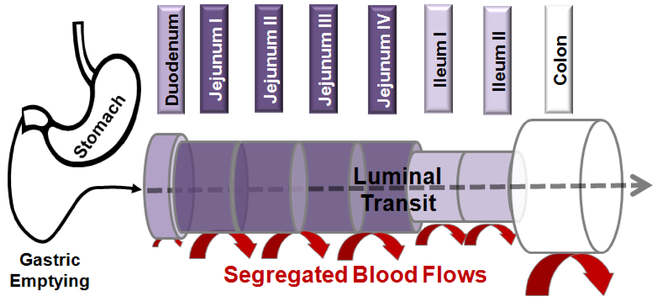
+/-5-fold

$P_{trans,Caco-2,int} = 2.482 \times 10^{-2} P_{PAMPA,int}^{0.6225}$

$-7 < \log P_{intrinsic,PAMPA} < 0.5$

1. Fenneteau F. 2007, Proc. Appl. Math. Mech. 7; 1121905-06.
2. Oliver R. 1998 J. Pharm. Sci; 87(5):634-9.
3. Sugano K. 2009; Int. J. Pharm. 23;368(1-2):116-22.

The ADAM Model



Regional Intestinal Permeability

	Duodenum	Jejunum I	Jejunum II	Jejunum III	Jejunum IV	Ileum I	Ileum II	Colon
P_{eff} Mouse	0.294	0.273	0.248	0.248	0.208	0.163	0.163	0.086

$$P_{trans} + P_{para} = P_{tot} \qquad P_{tot} \times ACC \times VE = P'_{tot}$$

$$P_{villi} = (1/P'_{tot} + 1/P_{UBL})^{-1} \qquad P_{UBL} = D_{eff} / h_{UBL}$$

$$D_{eff\_ubl} = f_{ionised} \bullet D_{ionised} + f_{neutral} \bullet D_{neutral} + f_{micelle} \bullet D_{micelle} \quad [3]$$

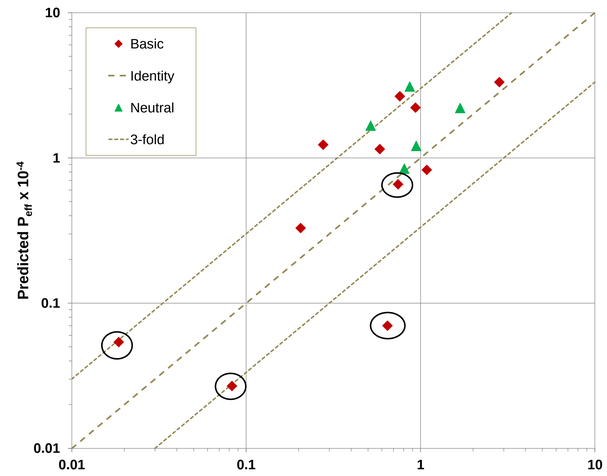
$$P_{eff} = P_{villi} \times FE$$

Model Input (Drug) Parameters and Mouse P_{eff} Values:

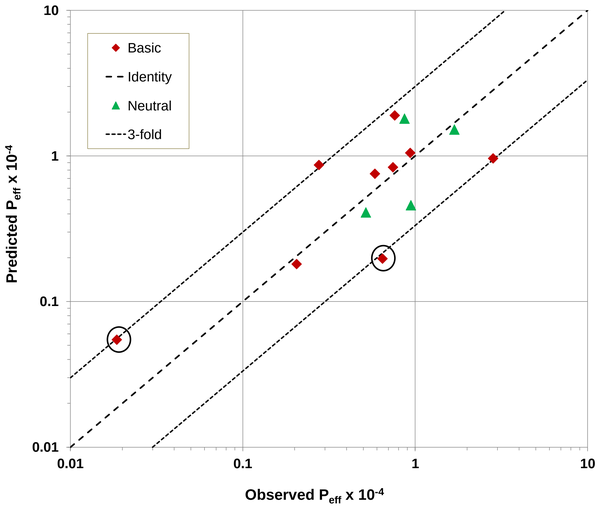
Drug	MWt.	Type	pKa	Log$P_{o:w}$	LogP_O	Obsd. Jejunal or Ileal [4,5,6] P_{eff} x 10^{-4} cm/s	Fold Predicted/Observed P_{eff} x 10^{-4} cm/s	
							Log$P_{o:w}$	LogP_O
Quinidine	324	DPB	4.2, 8.8	2.88	-1.56	0.74	0.89	1.13
Atenolol	266	MPB	9.4	0.16	-5.06	0.02	2.90	2.94
Metoprolol	267	MPB	9.75	1.95	-1.17	0.65	0.11	0.30
Talinolol	363	MPB	9.4	1.2	NA	0.08	0.32	NA
Cimetidine	252	MPB	6.8	0.48	-6.2	0.21	1.60	0.88
Daunomycin	528	MPB	7.85	1.83	NA	1.09	0.76	NA
Diazepam	285	N	3.4	2.9	-4.22	2.83	1.17	0.34
Loperamide	477	MPB	8.7	3.86	0.15	0.76	3.49	2.49
Ritonavir	721	N	2.45	4.3	-1.68	0.58	1.97	1.29
Verapamil	455	MPB	9.07	4.33	0.26	0.94	2.37	1.12
Vinblastine	811	MPB	7.4	5.32	-0.42	0.28	4.46	3.13
Darunavir	548	N	NA	2.47	NA	0.81	1.05	NA
Cyclosporin A	1203	N	NA	4.3	-3.21	0.94	1.28	0.49
Dexamethasone	392	N	NA	1.74	-4.05	0.87	3.58	2.08
Digoxin	781	N	NA	1.26	-5.78	0.52	3.22	0.79
Progesterone	314	N	NA	3.48	-2.55	1.69	1.31	0.90

DPB: Diprotic Base; MPB: Monoprotic Base; N: Neutral; NA: Not available;
Po: PAMPA intrinsic permeability; Underlined values indicate Ileal P_{eff} values

Results:



Predicted (using log$P_{O:W}$) vs. Observed Jejunal $P_{eff,mouse}$ Ileal Permeability values are circled



Predicted (using log$P_{0,PAMPA}$) vs. Observed Jejunal $P_{eff,mouse}$ Ileal Permeability values are circled

Conclusion:

The Mouse MechPeff model is reasonably successful in predicting the passive intestinal permeability of the studied drugs. Predicted permeability values were within **2-fold for 10 drugs** and within **4-fold for 5 drugs** out of the total 16 drugs. No specific trend in prediction quality was observed with respect to basic or neutral status.

4. Adachi Y. 2003, Pharm. Res. 20(8):1163-9.
5. Mols R. 2009; Drug Metab. Dispos. Jun;37(6):1334-7.
6. Holmstock N. 2010; Drug Metab Dispos. Sep;38(9):1407-10.