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Quantitative Prediction of Dermal Drug Absorption using MPML-MechDermA model: Relative Effects of Application Site on Rivastigmine Pharmacokinetics from a Transdermal Delivery System

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PURPOSE

A Mechanistic Dermal Absorption (MechDermA) model has been previously developed as part of the Simcyp platform [1]. The original model has been enhanced considerably to account for transient diffusion through tortuous lipid channels (inter-cellular) and permeation via transcellular (across corneocytes) pathways, referred to as the Multi-Phase Multi-Layer (MPML)MechDermA model. Furthermore, the model incorporates the effect of local skin physiology (layer thicknesses, lipid content, blood flow rates etc.) allowing drug application with a choice of 8 anatomical sites of the human body. Here, we assess the predictive performance of the MPML-MechDermA Model by simulating the relative effects of application site and size of transdermal delivery system (TDS) on systemic exposure of Rivastigmine; used for the treatment of mild to moderate dementia of the Alzheimer's type and dementia due to Parkinson's disease.

METHODS

A PBPK model was built using the physicochemical parameters and intravenous clearance parameters of Rivastigmine (Table 1).

Table 1. **Rivastigmine input parameters**

Input Parameter	Value	Source
Molecular Weight	250.34 g/mol	[4]
logP	2.3	[4]
pKa	8.89	[4]
B/P	0.9	[4]
Fu	0.6	[4]
CLiv	62.6 L/h	[5]
Vss	1.768 L/kg	Predicted in Simcyp

Two clinical study designs [2, 3] were simulated through virtual trials in the Simcyp simulator. TDS formulations were assumed to have zero order release rates (4.6, 9.5, 13.3 and 17.4 mg/day for the 5, 10, 15 and 20 cm^2 TDS respectively) based on the remaining TDS residues following 24 application from each study. For the anatomical location study [2], the 18 mg TDS was applied to three body sites (Thigh, Upper Arm, Back) and absorption profiles were simulated. For the study using variable TDS size [3], Upper Arm was used as the site of application for the product in all simulations. Four consecutive 24h applications were used to allow the simulations to reach steady state, for comparison with the clinical data. For both simulation scenarios the application period was set at 24h, and a washout period of 12h following the final dose was included, to match the clinical studies.

RESULTS

The MPML-MechDermA model predicted both mean exposure and observed variability following 24h applications to Back, Upper Arm and Thigh. Mean observed data were all within the 95% prediction intervals of the simulations for each application site. The extent of predicted inter-individual variability is consistent with the standard deviations reported for the observed data (Figure 1).

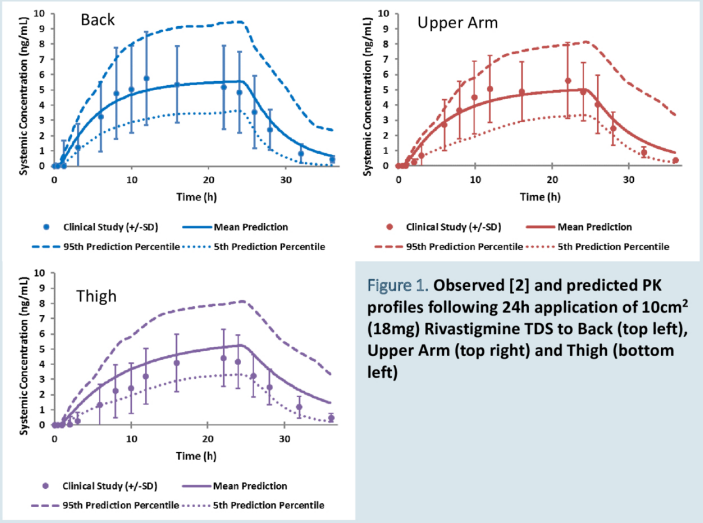

Figure 1. **Observed [2] and predicted PK profiles following 24h application of 10cm^2 (18mg) Rivastigmine TDS to Back (top left), Upper Arm (top right) and Thigh (bottom left)**

The model correctly predicted steady state exposure from the 15cm^2 and 20cm^2 TDS, but over-predicted exposure from the 5cm^2 and 10cm^2 TDS (Table 2). Predictions can be further improved through use of a first order or mechanistic drug release model, and by including nonlinear clearance of Rivastigmine. Rivastigmine is known to have capacity limited elimination due to saturation of metabolising enzymes [3].

Table 2. **Observed [2] and simulated pharmacokinetic parameters at steady state**

	AUC_{24h} Mean (SD)			Cmax Mean (SD)		
Dose	Observed	Simulated	PE%	Observed	Simulated	PE%
5cm^2	46.3 (17.2)	102.48 (33.16)	121.34	2.7 (1.2)	4.27 (1.38)	58.15
10cm^2	127 (41.4)	211.58 (68.47)	66.60	7.9 (2.9)	8.82 (2.85)	11.65
15cm^2	233 (83.2)	296.26 (95.87)	27.15	14.1 (6.3)	12.35 (3.99)	-12.41
20cm^2	345 (127)	387.56 (125.42)	12.34	19.5 (7.5)	16.15 (5.23)	-17.18

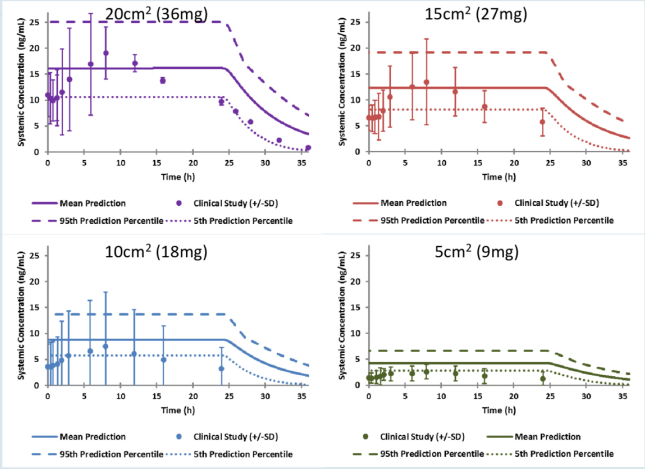

Figure 2. **Observed [3] and predicted PK profiles following multiple 24h applications of Rivastigmine TDS of different sizes and dose loadings**

CONCLUSION

The MPML-MechDermA model was able to predict the relative effects of application site on the dermal absorption of Rivastigmine. The model and/or parameters will be further refined to improve steady state prediction over the available dose range. The results demonstrate the potential of mechanistic bottom-up dermal absorption PBPK modelling in drug development. Such mechanistic simulations can help design, optimise and reduce clinical studies.

REFERENCES

[1] Polak et al. (2012), J. Pharm. Sci., 101:2584-2595. [2] Levèvre et al. (2007), J. Clin. Pharmacol., 47:471-478. [3] Levèvre et al. (2008), Clin. Pharm. & Therap., 83:1:106-114. [4] DrugBank, https://www.drugbank.ca/drugs/DB00989, [Accessed Aug 2017]. [5] Hossain et al. (2002), Clin. Pharmacokinet. 41(3):225-234.

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