Predicting local tissue concentrations after topical drug application with a physiologically-based pharmacokinetic model

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Background

For locally acting drugs that are applied topically, an estimation of the concentrations in dermal or sub-dermal tissues may be of significant importance to understanding the local effects of the drug. Techniques currently employed to measure local concentrations include biopsy, microdialysis and dermal open-flow microperfusion (dOFM), all of which suffer from being rather invasive techniques. Several attempts have been made to model local dermis concentrations of drugs following dermal absorption, the most notable being published by Kretsos (1), Ibrahim (2) and Anissimov (3).

Methods

A new Depth Resolved Dermis Model (DRDM) has been developed using a mechanistic, bottom-up approach (Figure 1). A preliminary version, integrated into a wider dermal absorption model based on the Simcyp MPML MechDermA model (4), has been constructed in R.

The dermis was split into four well-stirred compartments, with each compartment assigned depth specific physiology parameters obtained from the literature , including capillary and lymphatic vessel densities.

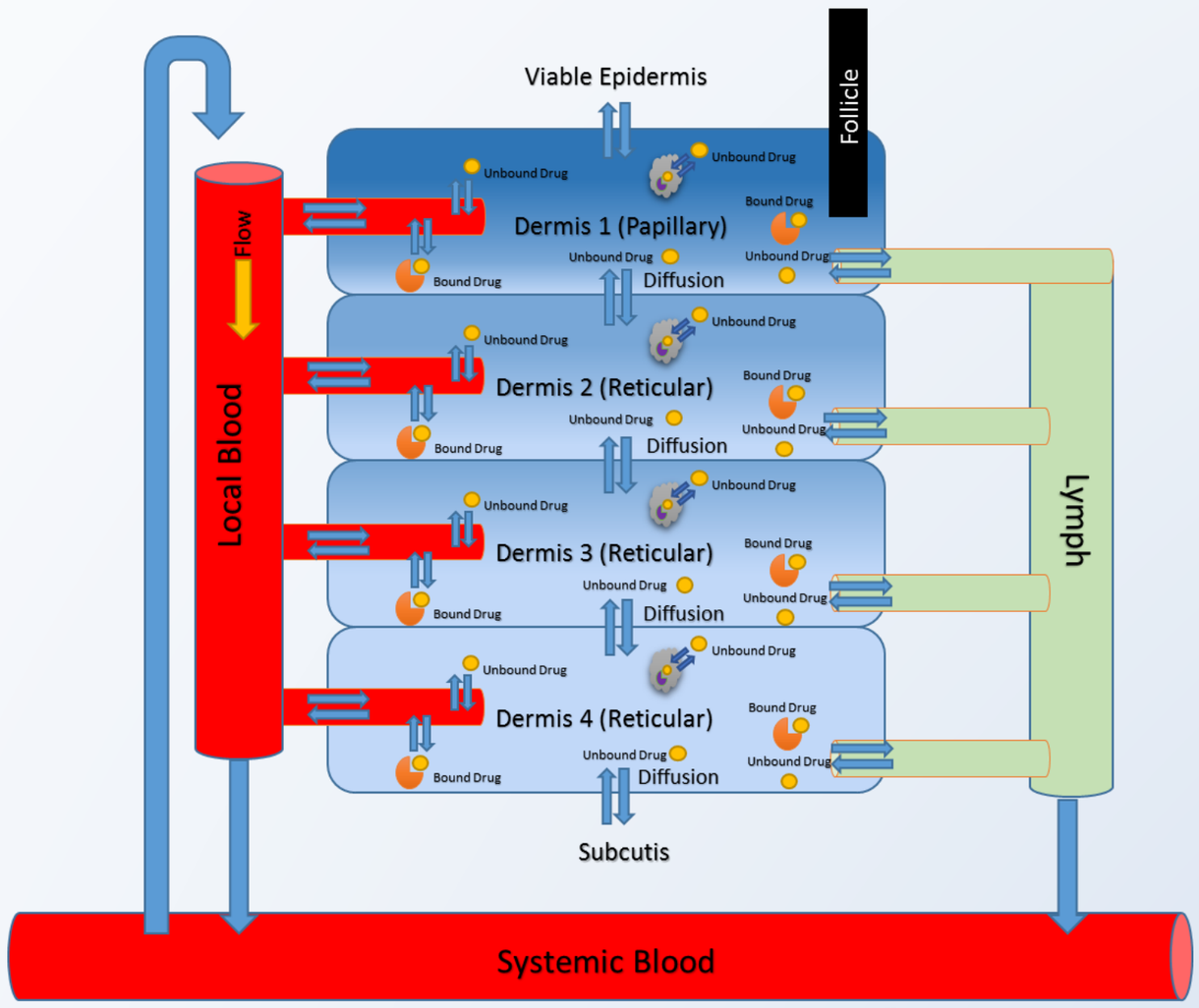

Figure 1 – Structure of the Depth Resolved Dermis Model (DRDM) = Cell

Passage of the drug between the interstitial fluid (ISF) and plasma is bidirectional and treated separately for bound and unbound drug. Only unbound unionized drug is allowed to permeate the endothelial wall, with all unbound drug and albumin bound drug able to pass by convection through small and large slits in the endothelium, based on the two-pore theory described by Rippe and Haraldsson. Each compartment has a local blood flow, which is linked to those adjacent. This allows drug to pass between compartments via blood perfusion before being removed to the systemic circulation; systemic blood is then recirculated.

Data produced by Schaefer and colleagues, who obtained depth-concentration profiles *in vivo* in the human dermis for 5 compounds (logP 1.61-6.3, MW 300 – 435) was used to verify the model. Methods used were input into the model, all parameters used were either experimentally measured or predicted using QSAR models.

Observed and predicted results are shown in Figure 2.

Results

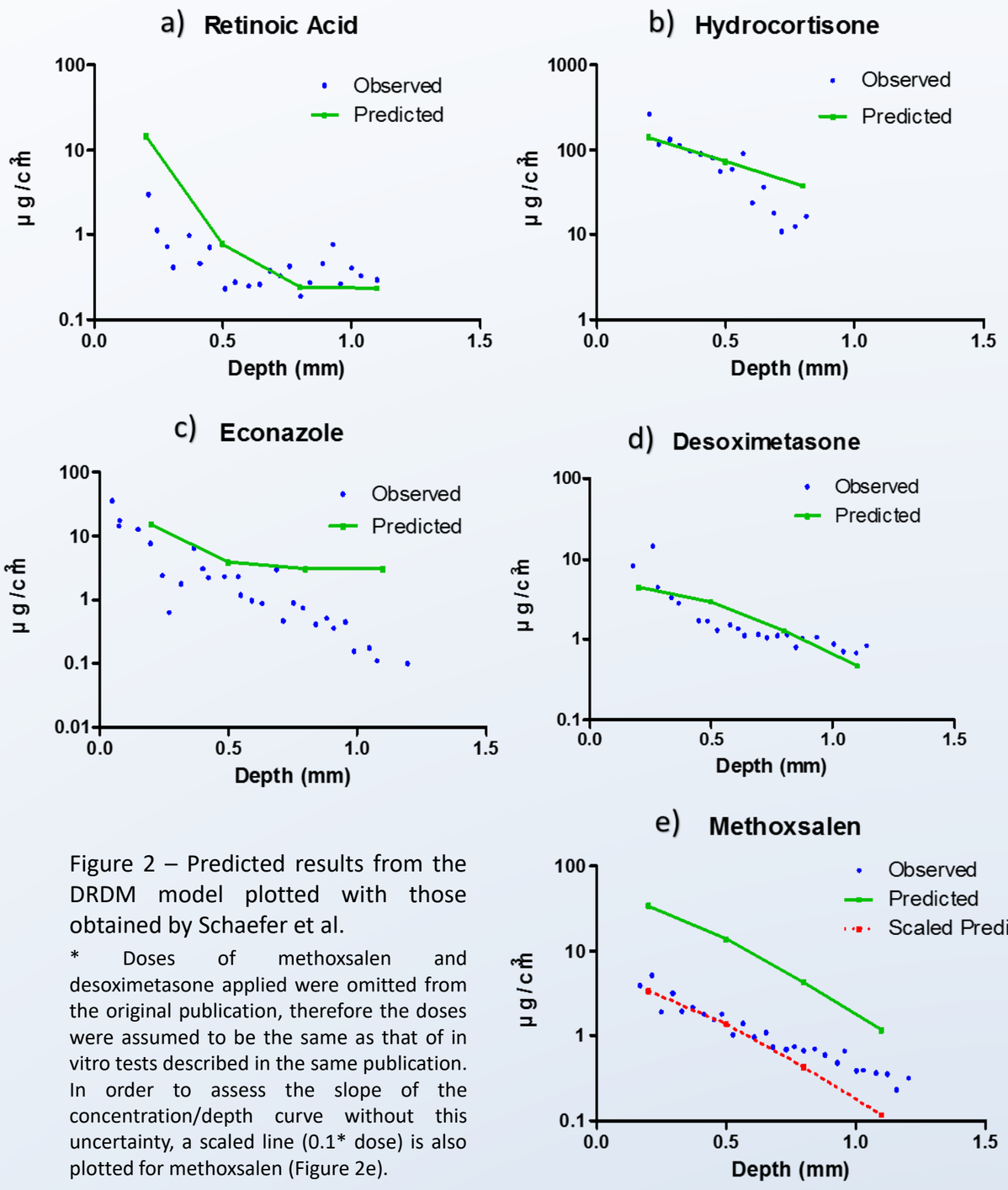

Figure 2 – Predicted results from the DRDM model plotted with those obtained by Schaefer et al.

* Doses of methoxsalen and desoximetasone applied were omitted from the original publication, therefore the doses were assumed to be the same as that of in vitro tests described in the same publication. In order to assess the slope of the concentration/depth curve without this uncertainty, a scaled line (0.1* dose) is also plotted for methoxsalen (Figure 2e).

Predictions of drug permeation through upper layers of the skin to the dermis, by the MPML MechDermA model were generally good. The DRDM model showed good recovery of the depth/concentration curves, an improvement on those shown by Anissimov (3) for the same data set.

Conclusions

An improved mechanistic dermis model has been developed based on the current state of knowledge in the area. When integrated into the Simcyp dermal absorption model, concentrations at specific depths were well predicted without any fitting or optimization.

Further verification of the model is required to investigate its ability to predict concentrations in specific phases i.e., ISF. Which would be required to inform or predict microdialysis and dOFM studies.

References

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3 Anissimov, Y. G. & Roberts, M. S. Modelling dermal drug distribution after topical application in human. *Pharm Res* **28**, 2119-2129, doi:10.1007/s11095-011-0437-2 (2011).

4 Martins, F., Patel, N., Salem, F., Jamei, M. & Polak, S. in *Gordon Research Seminar on Barrier Function of Mammalian Skin* (Waterville Valley, NH, USA, 2017).