#T1230-05-037

Predicting Depth Resolved Concentrations in the Dermis using PBPK modelling: Design, development and verification of the model with five drugs

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PURPOSE

For many topically applied products, the site of action is local. Therefore, in the product development process, or for bioequivalence assessment, it may be required to know concentrations in the dermis post-application.

Measurement of drug concentrations at these local sites is challenging and invariably involves invasive procedures such as biopsy or insertion of a dialysis probe.

Currently available models drug disposition in the dermis, such as those by Kretsos, Anissimov and Ibrahim do not take into account detailed physiology of the dermis such as depth specific differences in vasculature.

OBJECTIVES

The objective of this project was to develop a mechanistic Physiologically-Based Pharmacokinetic (PBPK) Model of the dermis using a bottom-up approach.

Once integrated into the SimCyp MPML-MechDermA Model, this model should be able to accurately predict concentrations of topically applied drug at specific depths within the dermis.

METHODS

A prototype model was created in R using a bottom-up approach. This was then integrated into a wider dermal absorption model based on the MPML-MechDermA model of SimCyp.

Physiology data was obtained form the literature allowing the papillary and reticular dermis compartments to be parameterised differently.

Albumin Bound drug is allowed to diffuse and pass between compartments.

QSAR models were used to describe diffusivity and permeability for each compound.

Two-pore theory was used to describe movement of albumin bound drug.

RESULTS

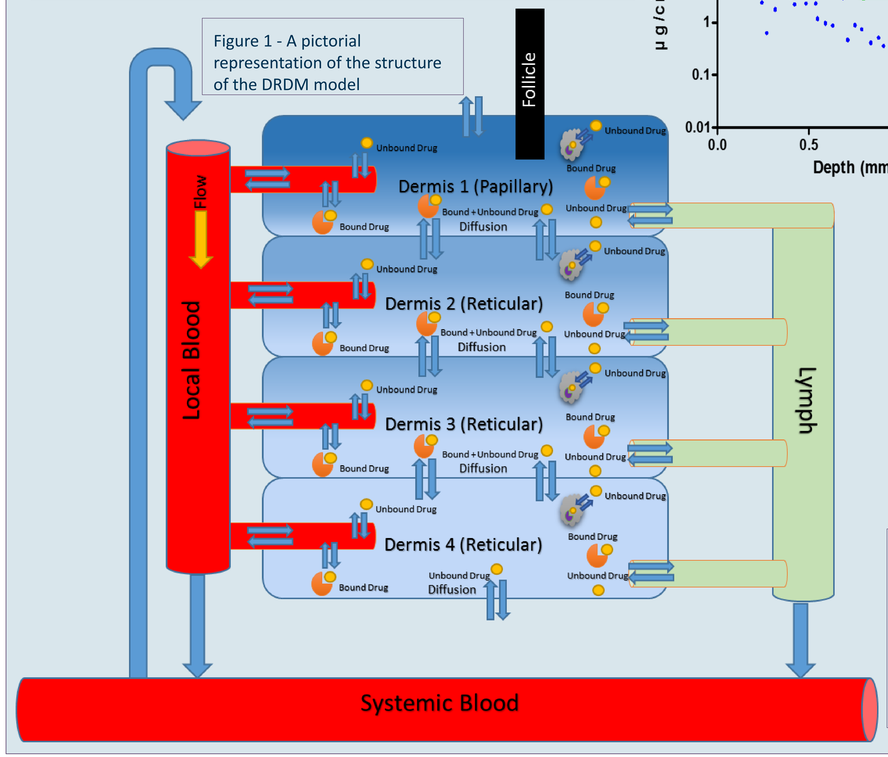
The Depth Resolved Dermis Model (DRDM) was verified for five compounds using data from Schaefer et al.

The data was obtained by extraction of drug from microtomed biopsy slices, giving a depth-concentration profile within the dermis.

Predicted vs observed results for each compound are plotted in Figure 2.

All parameters used were either predicted from physicochemical properties or experimentally measured.

Figure 1 - A pictorial representation of the structure of the DRDM model



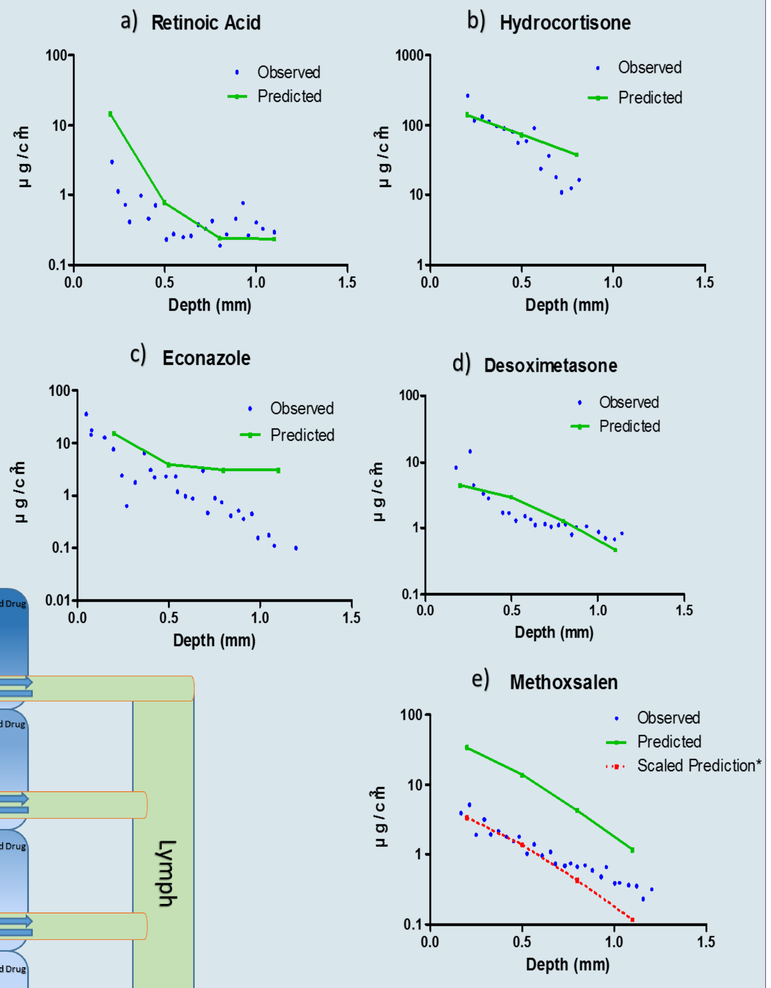


Figure 2 – Predicted results (green) from the DRDM model plotted with those obtained by Schaefer et al (blue)
* Doses of methoxsalen and desoximetasone applied were omitted from the original publication, therefore the doses were assumed to be the same as that of in vitro tests described in the same publication. 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).

CONCLUSIONS

- A mechanistic PBPK model of the dermis has been created which takes into account depth specific physiology and allows bound drug to diffuse and move between compartments.
- This model represents an improvement on those currently available in the literature.
- Input concentrations to the dermis from the MPML MechDermA model were accurate without fitting any parameters.
- Due to the mechanistic nature and realistic physiology of the model, it could be used to predict the effects of disease states, such as inflammation, in the future.

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