Quantitative description of the physiological changes in diseased skin and their incorporation into Physiologically Based Pharmacokinetic Models.

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Introduction

Physiologically Based Pharmacokinetic (PBPK) modelling has become a powerful tool in drug development.

What sets PBPK modelling ahead of other types of modelling, is the ability to simulate variability at the population level in a mechanistic manner. This is achieved by assigning variability to each physiological parameter, based on measured data from investigative studies. One major advantage of this approach, is the ability to extrapolate between populations.

The MPML Mech-DermA model, is a PBPK model implemented in to the Simcyp Simulator platform. Within this model is a large database of parameters describing the physiology of healthy skin in males and females, for 8 body sites. This model has undergone extensive verification for its ability to predict absorption of drugs to both local sites and systemically. In addition, data describing the physiology of other populations such as paediatric and geriatric have also been incorporated.

The aim of the current work was to identify and quantify parameters within the model that may differ between healthy skin and the skin of a patient with Psoriasis Vulgaris. Specifically this focused on the skin associated with the psoriasis plaque. By changing these parameters within the model, to capture differences in the absorption of drugs through plaque skin, as compared to that of a healthy patient.

Methods

An extensive literature search was conducted, parameters were collected for which quantitative data was available describing differences between the skin of healthy patients and that of a psoriatic plaque. Focusing on those that may affect the absorption of drugs in to and through this skin.

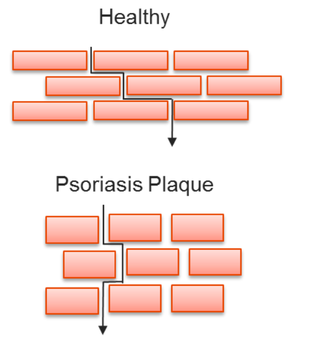
Two examples, are given for physiology parameters which have an effect on the absorption of a model drug.

Methoxsalen was used as a model compound, and a single dose scenario was considered.

Results

Parameters in the Model Modified to Simulate a Psoriasis Plaque:

- ↑ Stratum Corneum intercellular space and lipid amount
- ↑ Corneocyte Thickness
- ↓ Corneocyte Surface Area
- ↓ Stratum Corneum Hydration
- ↑ Epidermal Thickness
- ↑ Blood Flow (Dermis)
- ↑ Lymph Flow (Dermis)
- ↑ Capillary Exchange Surface Area and Diameter (Papillary Dermis)



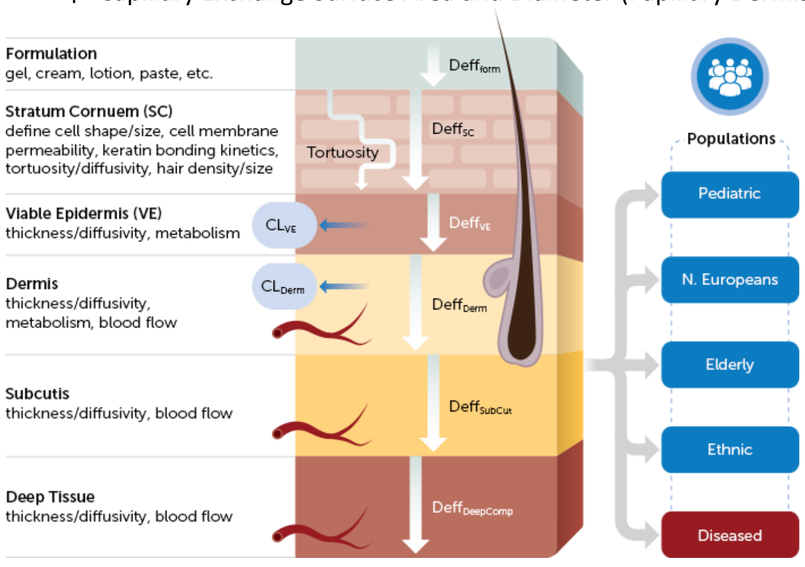


Figure 1. Structure of the MPML MechDermA Model. (not to scale)

Tortuosity

Based on the dimensions of corneocytes measured in the psoriatic plaque vs that of healthy skin. (1,2), utilising the theoretical equation derived by Johnson et al (3), the tortuosity of the diffusion pathway through the stratum corneum is predicted to be 2.2x lower. This results in around 20% higher Cmax in the Dermis. (Figure 2)

Results

Keratin Binding

Data from Anigbogu et al (4) found 2.2x more methoxsalen in the Stratum Corneum at equilibrium for a psoriasis plaque as compared to healthy skin. The model was used to predict what change in keratin binding would be required to recover this data. Figure 3 shows the equilibrium uptake of methoxsalen for different fraction unbound values. Change from the predicted fraction unbound value (red) of 0.203, to 0.148 (purple), recovered the experimental data. This corresponds to roughly 1.45x more keratin in the stratum corneum.

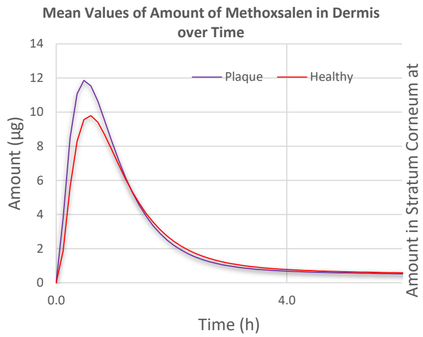


Figure 2

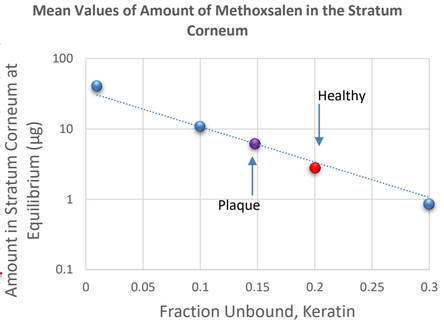


Figure 3

Conclusions

Some important model parameters for absorption of drugs through a psoriatic plaque have been identified.

Further verification of the model should include comparison of the compiled physiological changes against clinical data.

Further work to quantify changes in these parameters experimentally is required to fully understand and estimate the changes in absorption.

References

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