Mechanistic Physiologically-Based Pharmacokinetic Modelling for Prediction of Dermal Absorption in Psoriatic Patients

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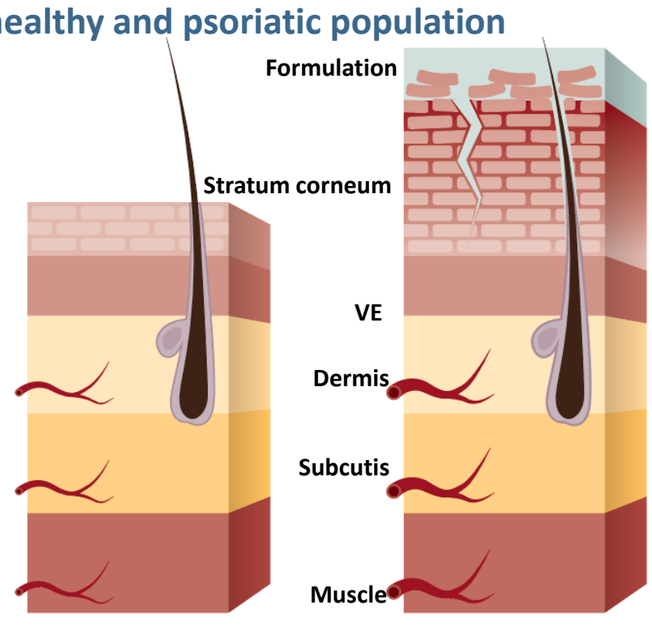
Abstract

Psoriasis is a chronic autoimmune inflammatory disease. The disease modified skin is characterised by epidermal hyperplasia, presence of cracks, leukocyte infiltration, inflammation, increased vascularity in dermis, red patchy and scaly skin at affected areas [1,2]. There are five main types of psoriasis: plaque, guttate, inverse, pustular, and erythrodermic [3,4]. Plaque psoriasis, also known as psoriasis vulgaris, makes up about 90% of cases. It is considered to be a disease with genetic association triggered by environmental factors. However, the origin and exact mechanism of disease or its progression is poorly established. Development of the *in vitro, in vivo* and *in silico* models mimicking psoriatic skin is crucial to predict and understand the dermal absorption of chemicals through skin affected by psoriasis. To the best of our knowledge, the Multi-phase multi-layer (MPML) Mechanistic Dermal Absorption (MechDermA) model is unique and the only available physiologically-based pharmacokinetic model facilitating dermal drug absorption prediction in psoriatic skin.

Methods

Skin physiology - PubMed searches were conducted using the search terms: *psoriasis, PASI, skin crack, psoriasis severity, blood flow, stratum corneum (SC) thickness, SC hydration, viable epidermis (VE) thickness, epidermis thickness and dermis thickness*. Papers were selected for review if they were published in English, Portuguese, or Spanish between 1969 and April 20, 2017, and focused on skin affected by psoriasis. Cracks, which are fissures present in SC affected by psoriasis, are considered a cut path/route for drugs. We did not find any data to describe the number and dimension of these structures. As an alternative, the cracks dimensions and their number per cm^2 were determined by analysis of images derived from available publications. Photomicrographies taken through an optical microscope or similar devices were analyzed using the ImageJ software [R]. Caffeine was used as a model drug for the assessment of percutaneous absorption in healthy and psoriatic population. 10 mg of drug in a solution gel (viscosity =1000cP) formulation was applied on 50 cm^2 cheek/face site. A virtual population of 100 subjects for each simulation was used and the duration of application was set to 2 hours.

Figure 1: MPML_MechDermA model healthy and psoriatic population



The SC was modelled as a brick-and-mortar structure where bricks (corneocytes) are cuboid embedded within the mortar of intercellular lipid matrix. The corneocyte is composed of water and protein core encapsulated within a lipid envelope. The model can simulate partitioning and absorption through hair follicular (HF) pathway depending on affinity for sebum and molecular size. While the drug diffuses through intercellular lipid matrix, depending on the drug to cell affinity and the concentration gradient, it can permeate into or out of the cells. The adsorption can be modelled as steady state using a binding parameter (fu_{SC}) or transient nonlinear adsorption/desorption kinetics (Kon/Koff). The drug present in the lipid matrix can diffuse to the next layer of SC. From the last layer of SC drug partitions into the VE depending on SC:VE partition coefficient. Blood flow to the dermis was modelled as a function of cardiac output, body weight and body surface area as per the Simcyp Simulator (V17) (Figure 1).

Results

Figure 2 shows a comparison of absorption profile of 10 mg of caffeine, between healthy and psoriatic skins. Due to the hyperplasia we observe a 50% increase of Tmax, and 20% decrease of Cmax, and AUC in for the psoriatic skin. The Figure 3 shows the simulated impact of disease progression on percutaneous absorption of caffeine.

Results Cont.

Figure 2: Simulated plasma concentration of caffeine after healthy and psoriatic skins exposure to 10 mg of drug loaded in gel.

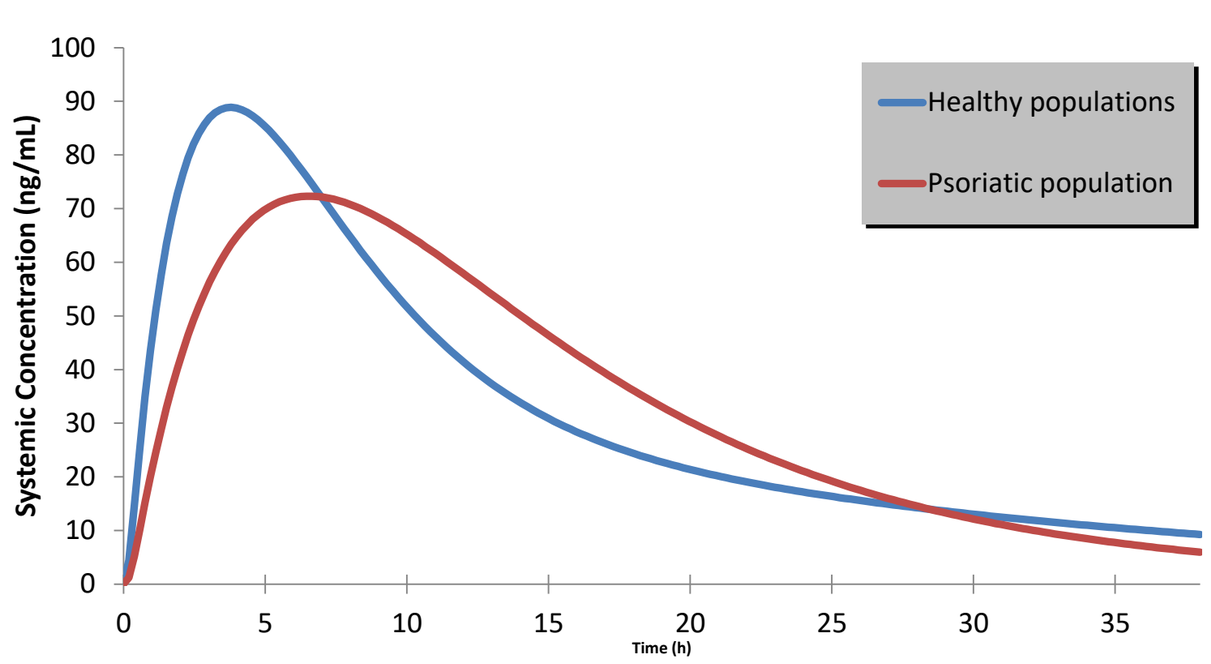
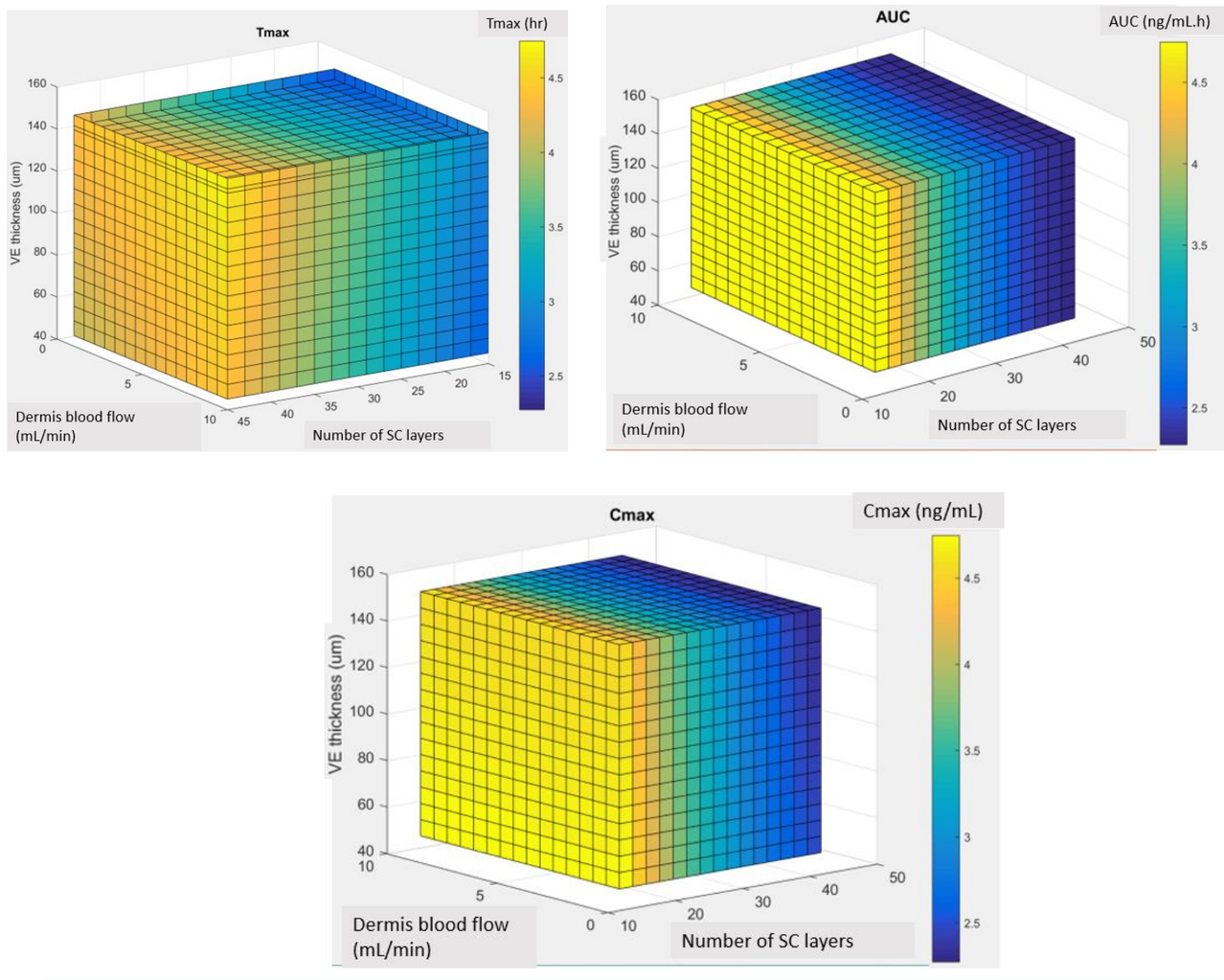


Figure 3: Impact of Psoriasis disease on percutaneous absorption of 10 mg of caffeine loaded in gel.



Conclusions

- The SC is a barrier to percutaneous absorption of caffeine and its thickness influences the systemic exposure; VE and dermis blood flow has minor impact on the caffeine absorption;
- Parameters such as the number of cracks, skin pH and SC hydration can significantly affect the percutaneous absorption of drug through the skin;
- Disease progression is an important factor for drug absorption;
- Performance verification is needed to confirm the model prediction.

References

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