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DERMAL PBPK MODEL FOR PSORIATIC SKIN: CLOBETASOL PROPIONATE CASE STUDY

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PURPOSE

Psoriasis is a chronic inflammatory disease often treated by drug products applied on the skin surface, and it is well accepted that disease-mediated physiological changes in the skin can significantly affect the permeation of active pharmaceutical ingredients (APIs) through the skin layers. Therefore, it is critical to understand how dermal pharmacokinetics (PK) can differ between healthy and psoriasis conditions. Dermal physiologically-based pharmacokinetic (PBPK) models can provide insight into drug partitioning in skin layers that are inaccessible or challenging to sample clinically. The purpose of this study is to demonstrate the utility of a dermal PBPK model in predicting Clobetasol Propionate (CP) dermal exposure in psoriasis patients. CP was selected as a case study based on the availability of dermal open flow microperfusion (dOFM) data in non-lesional and lesional skin in psoriatic patients [1].

METHODS

The Transdermal Compartmental Absorption and Transit (TCAT™) model within GastroPlus® v9.8.3 (Lancaster, CA, USA) was previously used to build and validate a dermal PBPK model for CP in non-lesional skin [2]. To account for the effect of psoriasis on skin physiology, the default values (that characterize healthy and non-lesional skin) of stratum corneum (SC) diffusivity, viable epidermis (VE) thickness and dermal blood flow (DBF) were modified considering 2-fold, 4-fold, and 5-fold increase, respectively, based on literature studies [3-8]. Parameter sensitivity analysis (PSA) was performed for each individual parameter, and for combination of parameters to assess the impact of skin physiology changes on model predictions. The predicted dermis concentrations were compared with the observed CP unbound concentrations in lesional psoriatic skin based on similar assumptions as in van Osdol WW et al, 2024 [1], [2].

RESULTS

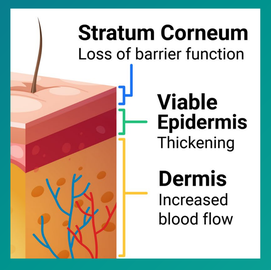
After introducing a 4-fold increase in VE thickness, a 5-fold increase in DBF, and a 2-fold increase in SC diffusivity relative to the healthy skin physiology, the model underpredicted observed CP concentrations in lesional skin, suggesting a need for further parameter optimization.

The impact of individual parameter changes was explored via PSA:

- **VE thickness (1.5 to 8-fold from default 61.4 µm),**
- **DBF (2 to 10-fold from default $9.89 \cdot 10^{-2}$ mL/min/g skin), and**
- **SC diffusivity (1.5 to 8-fold from default $1.104 \cdot 10^{-11}$ cm^2/s).**

The projections of CP concentrations (unbound) in dermal layer 14, corresponding to the depth of the dOFM probe, are shown in Figures A-C, respectively. Multifactorial PSA was performed (Figure D).

- The TCAT PBPK model for psoriatic skin reflects disease-related changes to skin layers.
- The model predicts clobetasol propionate dermal PK upon topical administration to lesional psoriatic skin.



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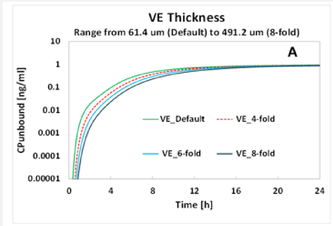
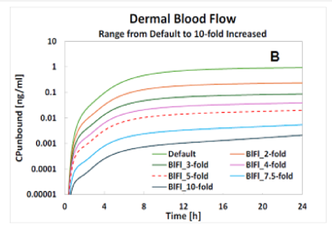
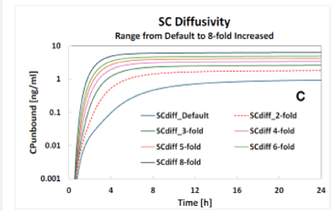
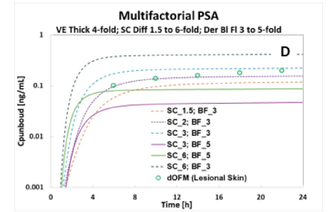
RESULTS









The ranges of individual parameters explored with PSA reflected the anticipated change for each parameter based on the literature. Increase in VE thickness, consistent with histology [3], was predicted to reduce CP dermis concentrations relative to non-lesional skin (Figure A). However, **increases in DBF and SC diffusivity were predicted to have significant impact on the CP dermis concentration (Figures B and C, respectively). The projections were overlaid in Figure D with CP lesional skin concentrations (Day 1) reported in the literature [1].**

CONCLUSION(S)

Our simulations of dermal PKs for psoriatic skin incorporate disease-related changes to the SC diffusivity, thickness of VE, and rate of DBF, and indicate how the disease state might alter drug permeation into the deeper skin layers. The multifactorial PSA (Figure D) shows that projections with 3-fold increase in DBF (5-fold was the initial estimate) and 1.5 to 3-fold increase in SC diffusivity (the 2-fold was the initial estimate) match closely the observed CP concentrations.

The PBPK model developed for psoriatic skin may be used to predict dermal PK across variations in formulation and stages of disease severity (equivalently, stages of response to therapy) [2].

FUNDING / GRANTS

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REFERENCES

[1] Bodenlenz M et al, 2016; [2] van Osdol WW et al, 2024;[3] Leroy M et al, 2015; [4] Khan A et al, 1987; [5] Mangion et al, 2024; [6] Osada M et al, 2004; [7] Maroto-Morales D et al, 2021; [8] Zolotas M et al, 2023