Dermal Drug Distribution in Normal and Psoriatic Skin Assessed in Silico via PBPK Modeling and Simulations

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PURPOSE

Plaque psoriasis is one of the most prevalent chronic skin diseases, affecting 2 to 3% of the world population [1], [2], [3]. Topical corticosteroid clobetasol propionate (CP) is commonly used for the treatment of plaque psoriasis [4].

We developed a modeling and simulation approach in GastroPlus® Transdermal Compartmental Absorption & Transit (TCAT™) to:

- Assess the magnitude of changes to the skin layers in psoriatic/lesional vs non-lesional/normal skin;
- Project CP dermal concentrations in non-lesional and lesional skin;
- Evaluate accuracy of the projections by comparison with literature data obtained via dermal open-flow microperfusion (dOFM) upon Dermovate® cream topical application on non-lesional (normal) and lesional psoriatic skin [5].

METHODS

The TCAT model simulates dermal and systemic PK of topically delivered APIs using an integrated system of rate equations. The TCAT model represents the skin as a collection of compartments, and the formulation (vehicle) is applied topically (Figure 1).

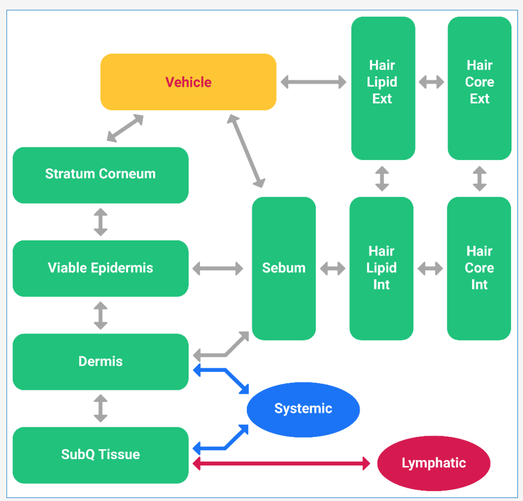


Figure 1: Scheme of TCAT™ module in GastroPlus®

RESULTS

Steps

- Dermal PBPK model for CP was developed for normal/non-lesional skin considering physicochemical and biopharmaceutical properties of the cream [6].
- The model was subsequently adapted to predict CP dermis concentrations in lesional psoriatic skin.

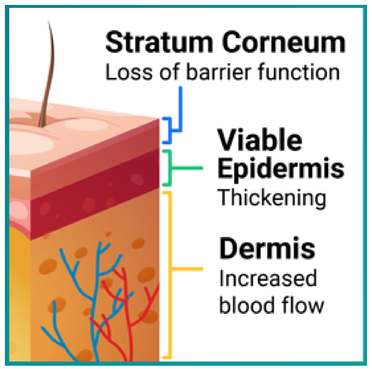


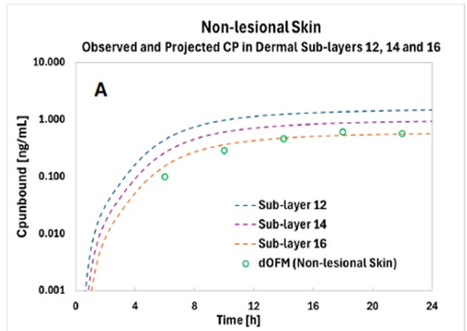
Figure 2: Schematic representation of the skin layers affected by psoriasis-related changes

- To account for psoriasis pathology, the default values representing normal/non-lesional skin for epidermal (VE) layer thickness, dermal blood flow (BF), and stratum corneum (SC) diffusivity were increased 4-fold, 5-fold, and 2-fold, respectively [7 - 12] (Figure 2).
- Parameter sensitivity analysis (PSA) was performed for individual parameters and combinations of parameters:

Table 1: Default values and PSA fold ranges for VE thickness, dermal blood flow, and SC diffusivity

Parameter	VE Thickness	Dermal BF	SC Diffusivity
Default TCAT Value	61.4 µm	9.89·10-2 mL/min/g skin	1.104·10-11 cm2/s
Individual PSA Ranges	1.5 to 8	2 to 10	1.5 to 8
Multifactorila PSA Ranges	4	3 to 5	1.5 to 6

The dermal drug concentrations projected in various sub-layers are overlaid with the observed concentrations obtained via dOFM in non-lesional/normal (Figure 3A, sub-layers 12, 14, and 16) and lesional skin (Figure 3B). The depth of the microperfusion probe corresponds to dermal sub-layer 14 in the TCAT model. Assuming 4-fold thickening in VE, the multifactorial PSA suggests 3-fold and 2-fold increases in dermal BF and SC permeability, respectively, for psoriatic skin (Figure 3B).



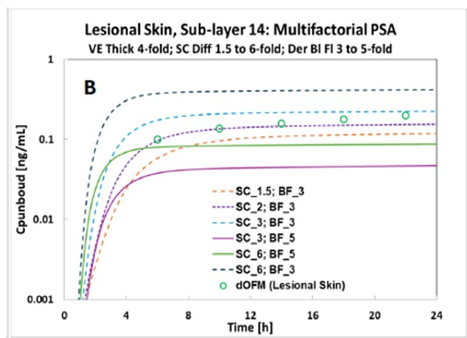


Figure 3: Simulated and observed CP dermal concentrations in normal/non-lesional skin, sub-layers 12-16 (A) and lesional skin, sub-layer 14 (B)

CONCLUSION

Modeling and simulation of dermal drugs is a valuable tool to:

- Assess BA of the API at the site of action that is inaccessible for routine sampling while systemic API concentrations are typically very low or undetectable;
- Account for disease-related changes in the skin that can significantly affect the permeation of APIs through the skin layers and systemic exposure.

Our TCAT model for psoriatic skin accounts for disease-related changes in psoriasis. The results indicate (a) the model's ability to reflect the reported CP concentrations in the dermis, and (b) the appropriateness of the psoriatic skin model implementation. Using CP as an example, the TCAT model projected dermis concentrations in non-lesional and psoriatic skin.

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