PBPK modeling of percutaneous pharmacokinetics for tazarotene and tretinoin creams: applicability and challenges

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OBJECTIVES

- To develop mechanistic dermal PBPK models for marketed tazarotene and tretinoin topical creams describing the skin and systemic disposition of tazarotene and tretinoin.
- To identify product critical quality attributes (CQAs) of the marketed tazarotene and tretinoin topical creams impacting tazarotene and tretinoin local and systemic bioavailability.

BACKGROUND

- Dermal physiologically-based pharmacokinetic (PBPK) modeling is a quantitative approach that allows for the prediction of skin permeation of active pharmaceutical ingredients (APIs) following topical application of dermatological products.
- Its predictive power stems from the integration of information on the physicochemical properties of the API, formulation attributes and skin physiology parameters.
- However, processes of metabolism, protein binding at different skin layers and clearance from dermis via routes including blood and lymph flow may pose challenges towards reliable predictions.

METHODS

The Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MPML MechDermA) model within the Simcyp® Simulator v19 (Certara, NJ, USA) was used to describe the tazarotene and tretinoin skin absorption following application of marketed products in virtual healthy subjects. Minimal PBPK models were developed to describe the systemic disposition of tazarotene and tretinoin. Public databases/resources[1-5] and drug application data were used for model development. All parameters describing partitioning and diffusion between and within skin layers for tazarotene and tretinoin were derived using Quantitative Structure-Activity Relationships (QSAR) models within the Simulator unless otherwise mentioned. API metabolism was modeled as a linear process and metabolite tracking was not possible due to limitations posed by the MPML MechDermA model. API metabolism-related parameters were optimized based on skin distribution and plasma data available in drug applications. Tretinoin and tazarotene metabolism-related parameters, the stratum corneum (SC) to viable epidermis partition coefficient ($K_{SC:VE}$) and the permeability of API partitioning into the SC corneocytes were optimized based on skin distribution data extracted from the drug applications. Protein binding in various skin layers was either estimated by QSAR models embedded within the MPML MechDermA model or assumed to be equal to plasma protein binding. Information on formulation attributes for the topical creams were extracted from application data. Parameter sensitivity analysis was performed to identify model parameters that have a greater impact on skin/systemic bioavailability.

REFERENCES & DISCLAIMER

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RESULTS

Model performance assessment: the developed dermal PBPK models described observed plasma data reasonably well

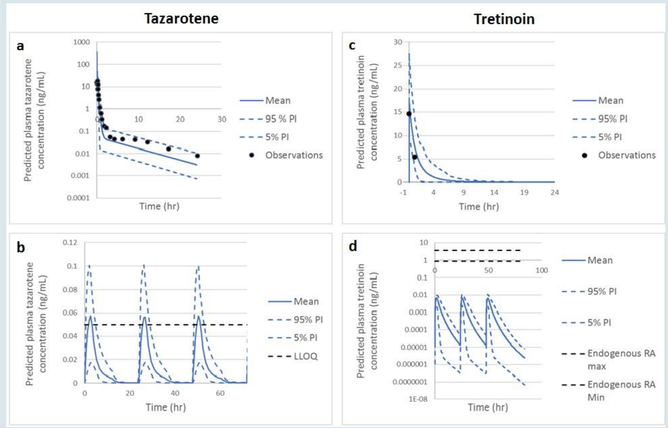

Figure 1. Mean (5%/95% PI) predicted tretinoin plasma tazarotene (a, b) and tretinoin (c, d) concentrations (ng/mL) versus time leveraging the developed systemic disposition and dermal PBPK models following intravenous (a, c) administration of the relevant APIs and skin application (b, d) of the tazarotene and tretinoin marketed products in virtual healthy subjects. Study design of the simulated studies were matched with the study design of in vivo PK studies corresponding to the marketed tazarotene and tretinoin products. (a) Observed data were from Ref 3 (intravenous infusion of 15 µg/Kg of tazarotene solution 0.01% w/v in 45% w/w ethanol over 20 minutes) and Ref 7 (intravenous infusion of 0.5 mg of tretinoin over 5 minutes) for panels (a) and (b), respectively. (c) LLOQ of the in vivo PK study is provided (interrupted black line). (d) Endogenous concentrations for RA are provided (interrupted black lines).

PI: prediction interval, LLOQ: lowest limit of quantification, RA: retinoic acid.

Skin metabolism is critical for reliable model predictions of local and systemic exposure

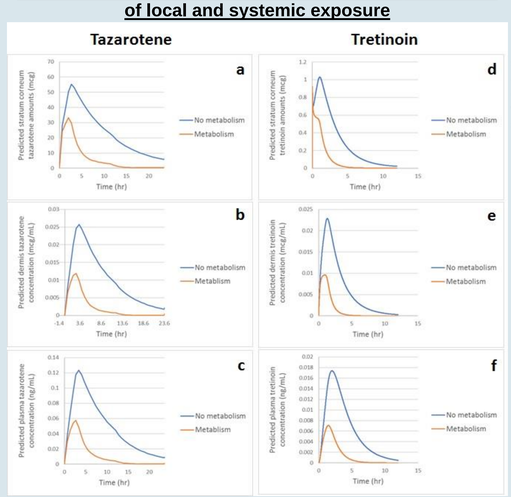

Figure 2. Mean predicted tazarotene (a-c) and tretinoin (d-f) PK profiles in stratum corneum (a, d), dermis (b, e) and plasma (c, f) leveraging the developed dermal PBPK models without and with the incorporation of skin metabolism.

pH, droplet size and drying rate impact dermis tazarotene concentrations following topical application of the tazarotene cream

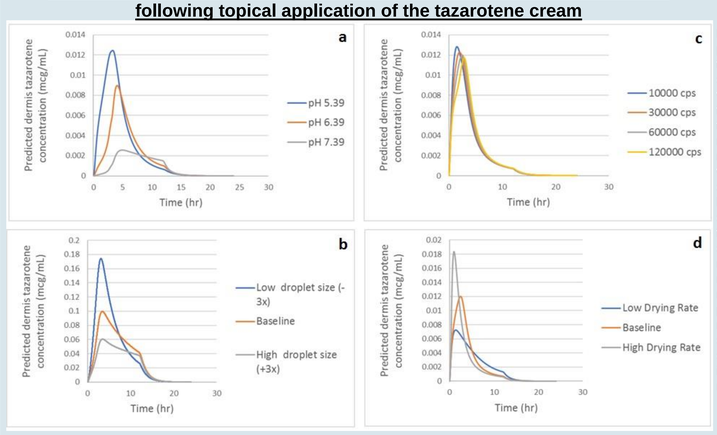

Figure 3. Mean predicted dermis tazarotene concentration versus time profiles following changes in the formulation pH (a), oil droplet size (b), apparent viscosity (c) and the drying rate (d) leveraging the dermal PBPK model for tazarotene cream. Droplet size (mean oil droplet radius) range: 1 (low) to 8.276 (high) µm, low/high drying rate: ± 10-fold the experimental value of the drying rate implemented for model development.

Apparent viscosity, droplet size and drying rate impact dermis tretinoin concentrations following topical application of the tretinoin cream

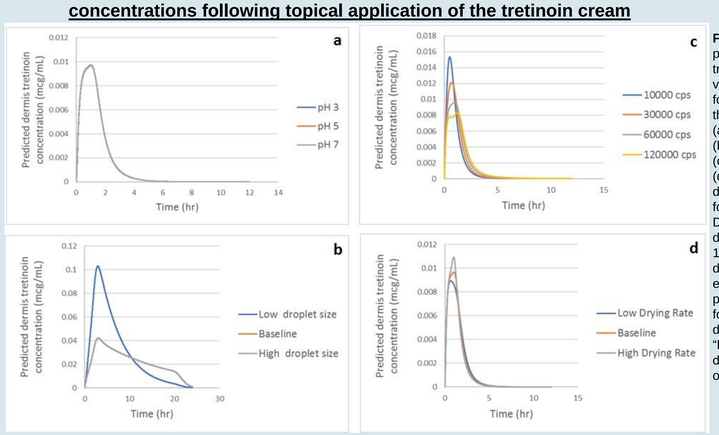

Figure 4. Mean predicted dermis tretinoin concentration versus time profiles following changes in the formulation pH (a), oil droplet size (b), apparent viscosity (c) and the drying rate (d) leveraging the dermal PBPK model for tretinoin cream. Droplet size (mean droplet radius) range: 1 to 6 µm, low/high drying rate: ± 20% the experimental drying profile implemented for model development. "Baseline" and "High droplet size" lines overlap in panel (b).

CONCLUSIONS

- The developed dermal PBPK models described tazarotene and tretinoin skin permeation and systemic disposition following product application.
- Droplet size, apparent viscosity (for tretinoin only), drying rate, and formulation pH (for tazarotene only) were predicted to impact local (dermis) API bioavailability.
- These findings can be used to support the development of product-specific guidances by informing in vitro characterization approaches and reduce the need for in vivo studies within the product development program.
- The work presented here exemplifies the unique role of PBPK modeling and simulation in evaluating the impact of formulation differences between products on local API exposure that may not be feasible to obtain through an in vivo study. PBPK modeling and simulation can also be used to support alternative BE approaches in drug development programs.
- Future research should focus on verifying and validating model predictions on local bioavailability for tazarotene and tretinoin and on developing modeling platforms that allow characterization of API and metabolite biodistributions across skin layers.