Mechanistic Physiologically-Based Pharmacokinetic Modelling of Skin Permeation of Propylene Glycol from Clobetasol Propionate Cream Formulations with variable Propylene Glycol Content

A. Maciel Tabosa[1], Y. Dancik[1], K. Thakur[1], Y. Zhang[1], S. Rangappa[2], N. Murthy[2], E. Tsakalozou[3], P. Ghosh[3], S. Polak[1,4], J. Clarke[1]

[1] Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, UK.
[2] Topical Products Testing LLC, Mississippi, USA.
[3]Office of Research and Standards (ORS), Office of Generic Drugs (OGD), Center for Drug Evaluation and Research (CDER), US Food and Drug Administration (FDA), Silver Spring, Maryland, USA.
[4] Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland.

Background

- **Propylene glycol (PG)** is a widely used **inactive ingredient** in topical drug products, known for **enhancing percutaneous absorption** [1,2].
- Despite its widespread use, **quantitative understanding of PG skin permeation** across formulations with varying concentrations remains limited.
- Understanding PG permeation supports the characterisation of **inactive ingredient behaviour** and exploration of their **concentration-dependent impact on active pharmaceutical ingredient** (API) **absorption**.
- This study combines ***in vitro* permeation testing (IVPT)** with **physiologically-based pharmacokinetic (PBPK)** modelling to predict PG absorption across formulations with varying PG content.
- Incorporating **inactive ingredient behaviour** into **dermal absorption models** enhances predictive frameworks and may support rational **formulation design**.

Methods

In vitro Permeation testing (IVPT)

Tested formulations:

- Dermovate Topical Cream 0.05% (reference product)
- Four alternative formulations: **20%**, **40%**, **47.5%** (assumed to be same as the reference product; "Dermovate-match"), and **80%** PG content

Skin Absorption Model & Setup

- Human dermatomed skin (body site: assumed to be back, thickness: 171 mm (CV =14%)), 4 donors, 3 replicates each
- Cell type: Static Franz diffusion cells
- Area of application: 1 cm^2
- Receptor volume: 8 mL
- Receptor Solution**:** phosphate-buffered saline (PBS, pH 7.4)
- Sampling volume: 300 µL
- Duration of the experiment: 48 hours

Dose: 15 mg/cm^2

PBPK Modelling

- All simulations were carried out in Simcyp Simulator version 24 using the the Multi-Phase Multi-Layer (MPML) Mechanistic Dermal absorption (MechDermA) model, IVPT module.

1 Development
- Input of PG physicochemical parameters
- QSAR-based predictions of PG partition and diffusion coefficients
- QSAR-based predictions of skin anatomical and physiological parameters
- Parametrisation of the PG formulation
- Input of the IVPT setup

2 Optimisation

The stratum corneum lipid:vehicle partition coefficient ($Kp_{SClip:vehicle}$) was optimised, and the sebum:vehicle partition coefficient ($Kp_{sebum:vehicle}$) was scaled proportionally*.

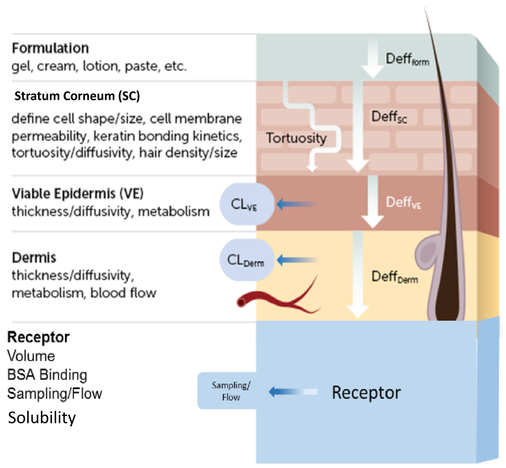
3 Evaluation

Model performance was assessed by comparing simulated PG profiles with IVPT study data from the reference product and alternative formulations.

4 Application

The optimised model was applied to simulate PG permeation from the four alternative formulations (20%, 40%, 47.5%, and 80% PG).

Figure 1. MPML MechDermA Model, IVPT module Structure

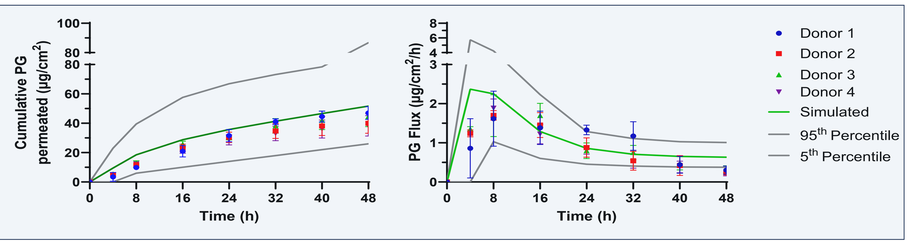


*$Kp_{sebum:vehicle}$ was scaled proportionally to the adjustment (optimization) applied to $Kp_{SClip:vehicle}$, under the assumption that both lipophilic compartments exhibit similar overprediction trends.

Results

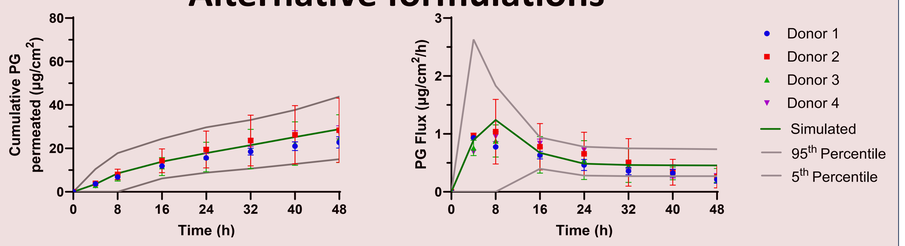
Observed (mean±SD, n=4, r=3) and simulated (mean is green line and 95% and 5% prediction intervals are grey lines) PG cumulative permeation and flux profiles for the reference product and alternative PG formulations.

Reference product

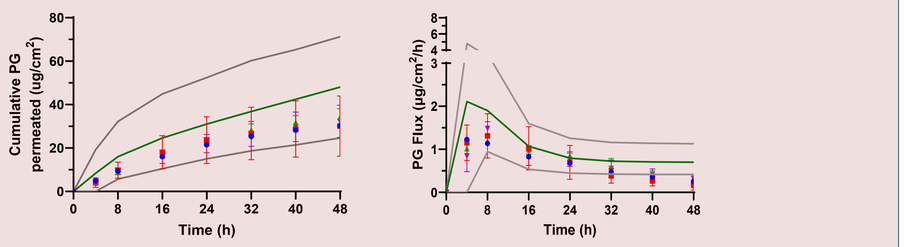


Alternative formulations

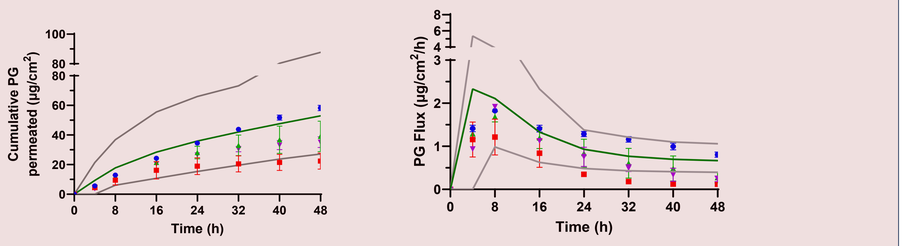
20% PG



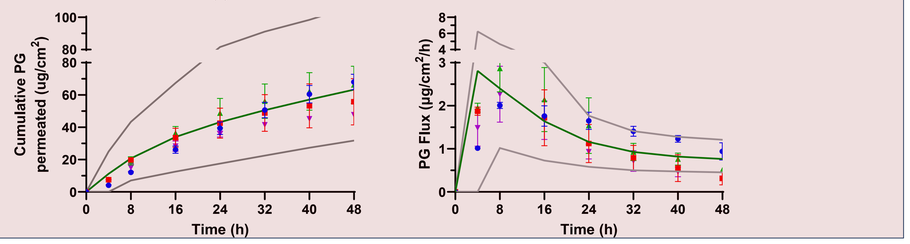
40% PG



Dermovate-match (assumed 47.5% PG)



80% PG



Predicted PG cumulative permeated amounts at 48 hours and maximum flux were within 2-fold of observed values for all formulations.

Conclusions

- Physiologically-based pharmacokinetic (PBPK) modelling accurately predicted *in vitro* skin permeation of propylene glycol (PG) from clobetasol-containing formulations.
- The model accurately captured PG permeation profiles across formulations of varying PG content.
- This framework enables integration of inactive ingredient behaviour into mechanistic models and may inform formulation selection when linked to drug permeation models.

Reference

[1] Lane, M.E., 2013. Skin penetration enhancers. International Journal of Pharmaceutics, 447(1), pp. 12-21
[2] Herkenne, C., Naik, A., Kalia, Y.N., Hadgraft, J. and Guy, R.H., 2008. Effect of propylene glycol on ibuprofen absorption into human skin in vivo. Journal of Pharmaceutical Sciences, 97(1), pp. 185-197.

Disclaimer

This work was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award U01FD007323 totalling $500,000 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government. This abstract reflects the views of the author and should not be construed to represent FDA's views or policies.

Gordon Research Conference on Barrier Function of Mammalian Skin, 2025, Waterville Valley, NH, USA.