Application of PBPK modelling to optimize IVPT study design and predict the impact of formulation changes on skin permeation

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Initial Model Development and Validation

Validated using Dermovate® Cream (Clobetasol Propionate, CbP) permeation data from literature.

Model Parameterisation with Experimentally Measured Inputs

Informed by measured formulation characteristics; Dermovate® Cream customized release data used to refine droplet permeability.

Model-Informed IVPT Study Design

Simulations used to make ab initio predictions and inform experimental protocol:

- ❑ *Sampling method (whole receptor vs. aliquot)*
- ❑ *Sampling frequency*
- ❑ *Solubility in receptor solution*

IVPT Studies Conducted

Studies performed using different receptor solutions with differences in CbP solubility:

- ❑ *Low (aqueous)*
- ❑ *Medium (enhanced with 0.5% BriJ)*
- ❑ *High (enhanced with 2% BriJ)*

Model Validation Against IVPT Data

Model validation, assessing its ability to capture permeation into receptor solution with varying CbP solubility levels.

Model Extension to CbP Alternative Formulations

Validated model extended to simulate CbP release and permeation from alternative formulations with altered Q3 property (globule size).

- **Bottom-up dermal PBPK model developed for Dermovate® cream using measured formulation characteristics, and the droplet permeability parameter informed by customized *in vitro* release data in the emulsion model. Model used to predict skin permeation ex vivo.**
- **Model used to inform IVPT study experimental design, including receptor solution selection and sampling frequency/volume.**
- **The model accurately captured reduced permeation and lack of sink conditions in low-solubility receptor solution, consistent with IVPT results.**
- **Validated model successfully captured reduced release and permeation from alternative formulations with altered globule size distribution (GSD) (10-fold increase) under ex vivo conditions.**

1. Background & Objective

In vitro permeation testing (IVPT) is used to assess skin permeation of topical drug products in both industry and academia. To ensure results derived from IVPT studies can address specific questions, studies must be carefully designed, taking into consideration critical factors such as the dose of the product used, selection of receptor solution in relation to sink conditions, sampling frequency, etc. In this work, dermal physiologically based pharmacokinetic (PBPK) modelling was used to aid the design of IVPT studies for Dermovate (clobetasol propionate, CbP) topical cream, 0.05%.

2. Methods

The dermal PBPK model for Dermovate cream was developed using the MPML MechDermA IVPT module within the Simcyp Simulator (Version 23, Release 2). A bottom-up approach was employed, with formulation parameters informed by physicochemical and structural (Q3) characterization data of the cream. CbP skin partition and diffusion coefficients were predicted using QSAR methods implemented within the simulator. The droplet permeability parameter in the emulsion model was informed using *in vitro* release data from customized release study.

IVPT studies were conducted using dermatomed skin (male, back or thigh). Static diffusion cells with a 1 cm^2 diffusion area were used, and a dose of 15 mg/cm^2 was applied under un-occluded conditions. The selection of the receptor solution and sampling frequency/volume were informed by the simulation results.

Customized *in vitro* release studies were performed using a 0.45 µm nylon membrane. A 500 mg dose of cream was applied under occlusion, and the receptor solution consisted of a 60:40 propylene glycol-water mixture, in order to mimic the composition of the cream's continuous phase.

Dermovate matching and alternative creams were prepared in-house using the same composition as the Dermovate Cream. Dermovate matching had a similar GSD compared to Dermovate Cream, while the alternative has an altered GSD achieved by modifying homogenization speed/duration.

3. Results and Discussion

Figure 1. The initial model validated by simulating Lehman 2014 IVPT study

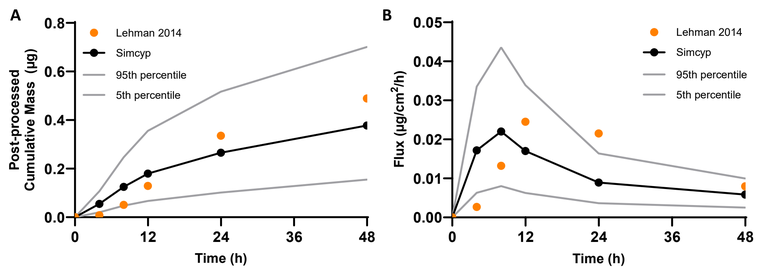
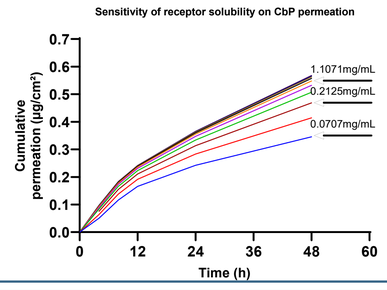


Figure 2. Sensitivity analysis of CbP solubility (receptor)



The initial model was validated against Lehman 2014 (Figure 1A,B), with a Predicted/Observed (P/O) ratio of 0.77 for cumulative permeation (Figure 1A). The model was utilized to inform IVPT study design:

- Sensitivity analysis (SA) showed increased permeation with CbP solubility in the receptor solution up to 1-2 mg/mL (Figure 2).
- Sampling frequency/volume were considered to ensure quantifiable levels (above LLOQ) in most cells across all time points in simulations (Table 1).

Model-informed IVPT studies were conducted: 1. using receptor solutions with low (only PBS, 0.07 mg/mL), medium (PBS + 0.5%Brij, 0.223 mg/mL), and high CbP solubility (PBS + 2%Brij, 1.659 mg/mL), and 2. a 0.3 mL aliquot sampling every 8 hours (h) over 48 h was used in the IVPT design (Table 1).

Table 1. Percentage of cells predicted to reach the LLOQ level for CbP (10 ng/mL) at different timepoints in a simulated IVPT study using 2% Brij S20-SO-(MH) in PBS as receiving solutions.

Sampling intervals	Sampling method	4h	8h	12h	16h	20h	24h	28h	32h	36h	40h	44h	48h	52h	56h	60h	64h	68h	72h
Every 8h	Whole receptor	-	48%	-	48%	-	53%	-	58%	-	61%	-	63%	-	64%	-	64%	-	65%
Every 4h		7%	8%	5%	5%	6%	6%	7%	8%	8%	8%	8%	8%	8%	8%	7%	6%	6%	6%
Every 8h ✓	0.3 mL Aliquot sampling	-	47%	-	83%	-	93%	-	96%	-	97%	-	98%	-	98%	-	99%	-	99%
Every 4h		7%	46%	64%	83%	89%	93%	93%	95%	97%	97%	98%	98%	98%	98%	98%	98%	98%	98%

Figure 3 shows predicted and observed CbP permeation profiles in receptor solutions with differences in CbP solubility. Despite variability, permeation increased with increasing receptor solubility in the IVPT studies, consistent with sensitivity analysis. Simulated profiles closely matched observed data. For skin retention, P/O ratios for high and medium solubility groups were within the predefined 2-fold acceptance criteria, while P/O ratio for low solubility group was 2.33.

Figure 3. Simulation vs. observed permeation of CbP from Dermovate Cream into different receptor solutions. Observed data represent mean values; error bars indicate standard deviation (n = 4 donors, 3 replicates each).

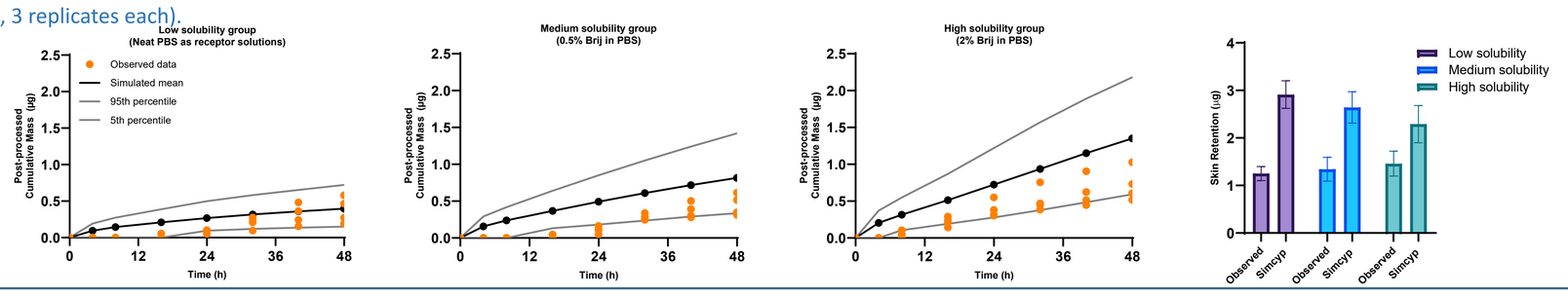
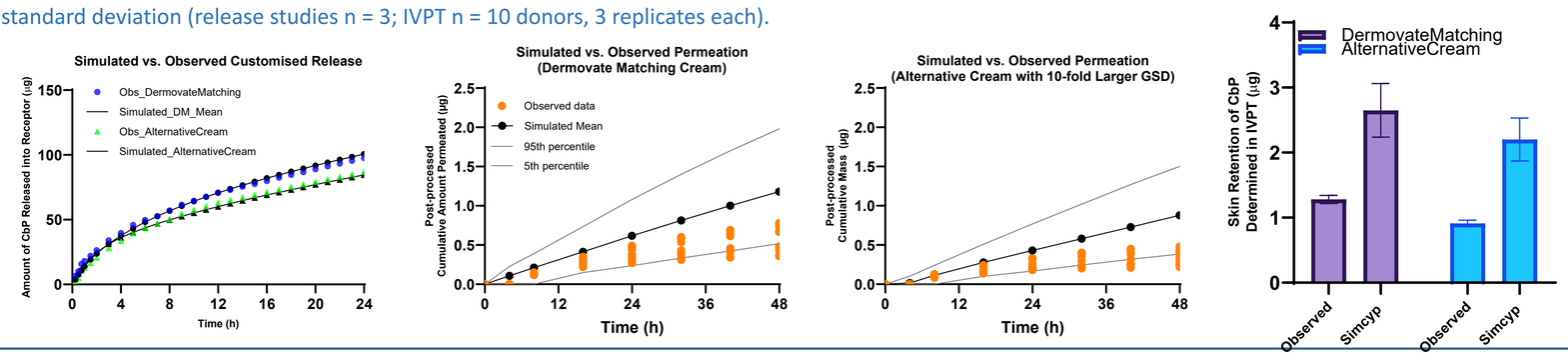


Figure 4 shows that the alternative cream with a 10-fold larger globule size was predicted by the model to have lower release compared to the Dermovate matching cream. This prediction was confirmed by the experiment results, which showed reduced in vitro release from alternative cream (Figure 4). The simulation also predicted 1.3-fold higher permeation for the Dermovate matching cream compared to the alternative cream, which aligned with the IVPT results showing a 1.7-fold higher permeation – further supporting the model's ability to distinguish formulation-dependent differences in release and skin permeation.

Figure 4. Simulation vs. observed release and permeation of CbP from Dermovate Matching Cream and Alternative Cream (10-fold larger GSD). Observed data represent mean values; error bars indicate standard deviation (release studies n = 3; IVPT n = 10 donors, 3 replicates each).



4. Conclusions

This present work demonstrates that dermal PBPK models can be used to support the development and evaluation of topical drug products. By accurately predicting the impact of key factors such as receptor solution solubility, sampling volume, and sampling frequency, among other, PBPK modeling serves as a valuable tool for optimizing IVPT study designs. The model also predicted changes in *in vitro* release and skin permeation resulting from differences in Q3, providing valuable mechanistic insights into guiding topical product development.

5. References

Lehman PA, Franz TJ. Assessing topical bioavailability and bioequivalence: a comparison of the in vitro permeation test and vasoconstrictor assay. Ther Innov Regul Sci. 2014

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