Simulating the Effect of Propylene Glycol on Acyclovir (Zovirax® Cream, 5%) Permeation Across the Skin Using a Physiologically Based Pharmacokinetic (PBPK) Model of *In Vitro* Flow-through Skin Permeation

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Introduction

An adequately validated *in vitro* permeation test (IVPT) can provide a mechanistic understanding of local drug bioavailability following application of topical dermatological products. IVPT is routinely used during formulation development of topical products and is recommended as part of an *in vitro* characterization-based approach for establishing bioequivalence (BE) in the recently published FDA Draft Guidance on Acyclovir (Topical cream, 5%).[1]

The present study aimed to develop a mechanistic "bottom-up" PBPK model integrating drug product quality attributes to predict *in vitro* permeation of acyclovir commercial cream, Zovirax® Cream 5% (approved in the U.S) applied on excised human skin and to understand the role of propylene glycol (PG) in influencing the acyclovir skin permeation.

Methods

The model was developed using the Multi-Layer Multi-Phase Mechanistic Dermal (MPML-MechDermA)[2] model implemented in the Simcyp® Simulator Version 19. Key input model parameters such as those related to physical and structural characterization of the Zovirax® Cream, 5% (Table 1) were obtained from Murthy 2015.[3] *In vitro* skin permeation data for model verification were obtained from Shin et al.[4] All kinetic parameters such as partition and diffusion coefficients through various layers of skin were predicted by quantitative structure–activity relationship (QSAR) models available in Simcyp.

Two modeling approaches were explored to understand the effect of PG in influencing acyclovir skin permeation – (A) Static approach which included the effect of PG on the stratum corneum lipid:vehicle partition coefficient ($Kp_{sc\ lipids:vehicle}$) for acyclovir by calculating a single constant value for this parameter, and (B) Dynamic approach which assumed time-dependent increase in $Kp_{sc\ lipids:vehicle}$ as the result of the hypothesized PG skin permeation. Simulations were carried out using ten trials of six virtual donors (healthy volunteers, outer forearm application site) following application of 15 mg/cm^2 of Zovirax® Cream, 5%.

Table 1. ***Input parameters for Zovirax® Cream, 5% in the PBPK model***

Properties	Zovirax	Comment
Vehicle molar volume (mL/mol)	41.05	Calculated, Formulation toolbox
Amount of drug product applied (mg/cm^2)	15.0	Murthy 2015[3]
Density of formulation (g/cm^3)	1.017	Murthy 2015[3]
Volume of formulation (mL)	0.0147	Murthy 2015[3]
Thickness of formulation (cm)	0.0147	Murthy 2015[3]
Viscosity (cP)	8360	Murthy 2015[3]
Volume of water phase (% v/v)	33.0	Roberts 2017[5]
Volume of PG (% v/v)	40.0	Trottet et al. 2005[6]
Volume of solid particle (% v/v)	4.14	Calculated from dose applied
Volume of dispersed phase (% v/v)	22.86	Calculated [100-(Vol of Water+PG+Solid Particle)]
pH of formulation after 2 h	7.00	Considering buffering effect of skin and formulation
Acyclovir amount dissolved in aqueous Phase (mg/g)	0.492	Murthy 2015[3]
Total acyclovir amount dissolved (mg/g)	1.354	Murthy 2015[3]
Acyclovir amount dissolved in dispersed Phase (mg/g)	0.862	Calculated (Total Amount Dissolved- Amount Dissolved in Aqueous Phase)
Ratio of acyclovir in dispersed/aqueous Phase	1.752	Calculated (Amount Dissolved in Dispersed Phase/ Amount Dissolved in Aqueous Phase)
Acyclovir solubility (mg/mL)	1.49	Assumed that the amount of drug determined by Murthy 2015 is dissolved in the volume of the aqueous phase
$Kp_{sc\ lipids:vehicle}$ (Effect of PG)	0.25	DI´EZ-Sales et al. 2005[7]
$Kp_{sebum:vehicle}$ (Effect of PG)	0.1017	DI´EZ-Sales et al. 2005[7]
Evaporation profile	User Input Profile	Murthy 2015[3]
Precipitation model	Growth Model	As implemented in Simcyp Simulator V19

Acknowledgment: Funding for this research work was made possible, in part, by the U.S. Food and Drug Administration through Grant 1U01FD006522. The views expressed in this poster do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

Results

The developed PBPK model was able to simulate the cumulative acyclovir amount permeated in the IVPT experiment using a flow-through diffusion cell. Using a static model that assumed the effect of the 40% PG on the stratum corneum lipid: vehicle partition coefficient ($Kp_{sc\ lipids:vehicle}$) for acyclovir, the model was able to capture the extent of acyclovir permeation (Figure 1A), however the shape of the profile was not adequately captured. When the time-dependent increase in $Kp_{sc\ lipids:vehicle}$ as the result of the hypothesized role of PG in skin permeation was considered, the model appeared to predict both the extent and kinetics of acyclovir permeation well (Figure 1B).[4] Simulated cumulative amount of acyclovir permeated through excised skin were most sensitive to the $Kp_{sc\ lipids:vehicle}$ and acyclovir solubility in the continuous phase of the formulation (Figure 2).

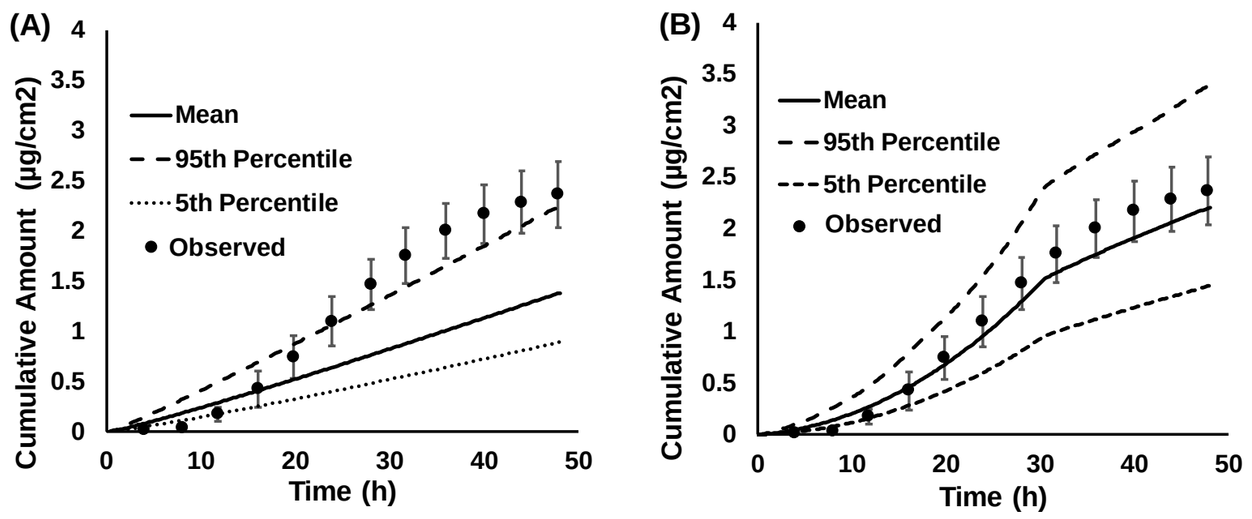

Figure 1. Mean cumulative permeation of Acyclovir following application of 15 mg/cm^2 of Zovirax® Cream, 5% (A) with constant stratum corneum lipid: vehicle partition coefficient and (B) with time-dependent stratum corneum lipid: vehicle partition coefficient considering the effect of propylene glycol on acyclovir skin permeation. Black circles with error bars (Mean ± SE, n= 6 donors with 4-7 replicates per donor) represent the observed data reported by Shin et al.[4]

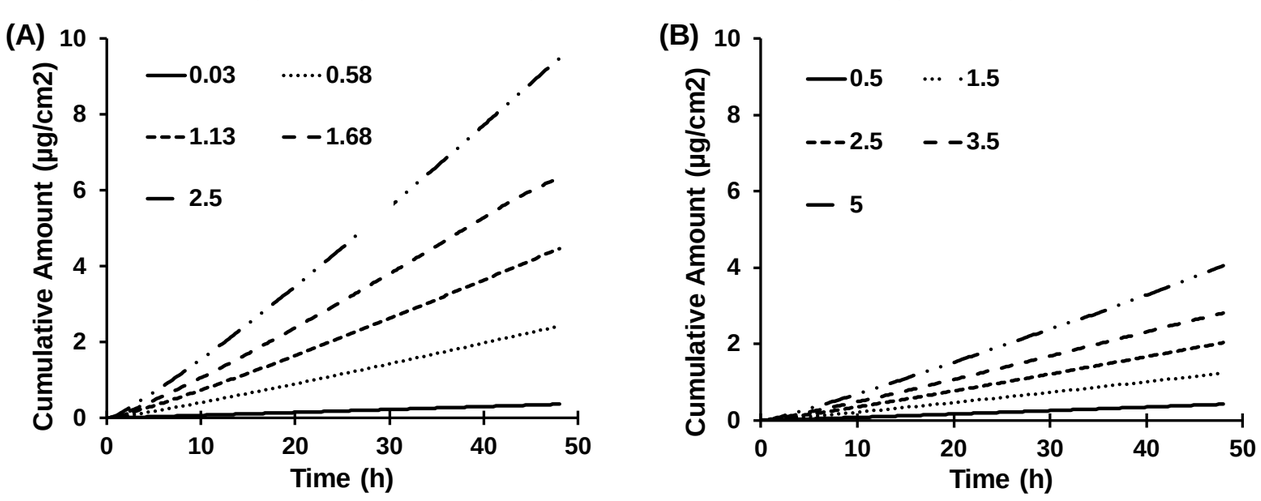

Figure 2. Sensitivity analysis of the impact of the formulation to stratum corneum lipids (Kpsc lipids:vehicle) partition coefficient (A) and of the acyclovir solubility (mg/mL) in the aqueous phase (B) on the cumulative acyclovir amount permeated in the receptor fluid. Kpsc lipids:vehicle was 0.25 and acyclovir solubility was 1.49 mg/mL in the final model (Table 1).

Conclusions

- The current study, using a limited dataset, illustrates the potential utility of PBPK models in understanding and interpreting the impact of specific inactive ingredients on drug permeation across the skin.
- Improvement in model predictability of skin permeation of the active ingredient when accounting for an inactive ingredient effect underlines the need to consider the interplay between the drug substance and key inactive ingredient(s).
- Acyclovir partitioning from the formulation to stratum corneum lipids and solubility of acyclovir in the continuous phase of the formulation were found to impact the cumulative acyclovir accumulation in the receptor solution.

References

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