Integrating Drug Product Quality Attributes in a Bottom-Up Physiologically Based Pharmacokinetic (PBPK) Model to Simulate *In Vitro* Skin Permeation of Acyclovir Commercial Formulations

Sumit Arora[1], Sebastian Polak[1,2], Masoud Jamei[1], Eleftheria Tsakalozou[3], Priyanka Ghosh[3], Khondoker Alam[3], Xin Liu[4], Sarika Namjoshi[4], Jeffrey Grice[4], Yousuf Mohammed[4], Michael Roberts[4]

[1]Certara UK Ltd, Simcyp Division, Sheffield, UK ,[2]Faculty of Pharmacy, Jagiellonian University Medical College, Poland,[3]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA.,[4]Therapeutics Research Centre, Diamantina Institute, University of Queensland, Brisbane, Queensland, Australia

PURPOSE

In vitro permeation testing (IVPT) is commonly employed in topical/transdermal formulation development and often provides a mechanistic understanding of drug permeation across skin. In addition, an *in vitro* characterization-based approach including IVPT has been recommended for establishing bioequivalence (BE) in the U.S. FDA Draft Guidance on Acyclovir (Topical Cream, 5%).[1] The present study aimed to develop a mechanistic "bottom-up" PBPK model integrating drug product quality attributes to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 creams, Zovirax® Cream 5% (approved in the U.S.) and Aciclostad® Cream, 5% (approved in Austria) following application on excised human skin. Furthermore, the model was used to understand the role of propylene glycol (PG) in the skin permeation of acyclovir from the Zovirax® Cream which has been reported to contain 40% w/w PG.[2]

METHOD(S)

The Multi-Layer Multi-Phase Mechanistic Dermal Absorption (MPML-MechDermA) model implemented in Simcyp Simulator Version 19 (Certara, UK) was used. All experimental data for model development and verification were obtained from the literature. Key model input parameters such as product quality attributes of Zovirax® and Aciclostad® Creams (Table 1) were obtained from Murthy 2015.[3] Two modeling approaches were explored to understand the effect of PG on influencing acyclovir skin permeation – (A) Static approach which included the effect of PG on the stratum corneum lipid:vehicle partition coefficient (Kpsc lipids:vehicle) for acyclovir by calculating a single constant value of this parameter, and (B) Dynamic approach which assumed time-dependent increase in Kpsc lipids:vehicle as the result of the hypothesized PG skin permeation. In vitro cumulative skin permeation profiles for these two commercial products used for model verification were reported by three independent laboratories.[3,4,5] 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® and Aciclostad® Creams.

RESULT(S)

Figure 1 shows the simulated and observed cumulative permeation of acyclovir following application of Zovirax® and Aciclostad® Creams on excised human skin using the static modeling approach. The developed PBPK model with inclusion of physical and structural characterization data of commercial formulations was able to simulate the cumulative acyclovir amount permeated and matched data from IVPT experiments reported by two laboratories[3,4]. However, the simulated IVPT data underpredicted the extent of acyclovir permeation compared to the observed IVPT data reported by Roberts 2017[5] probably due to the partially occluded conditions under which the IVPT was conducted. Occlusion may influence the evaporation of volatile components from the applied formulations, thereby affecting permeation of acyclovir through excised skin. When the time-dependent increase in stratum corneum lipid:vehicle partition coefficient as the result of the hypothesized PG skin permeation was considered under the dynamic modeling approach, the model adequately predicted both the extent and kinetics of acyclovir permeation from Zovirax® Cream (Figure 2) observed in all three laboratories.

CONCLUSION(S)

The current study shows that the developed PBPK model when adequately parameterized with regard to drug product quality attributes can be used for "bottom-up" predictions of *in vitro* skin permeation of acyclovir. The present model, using a limited data set, can also be used to understand the permeation enhancing effect of PG, which is commonly used in topical/transdermal formulations. The modeling approach described here warrants further verification/validation with additional drug products.

REFERENCE(S)

1. U.S. Food and Drug Administration. Draft Guidance on Acyclovir (Topical Cream, 5%) 2016.

2.Trottet et al. International Journal of Pharmaceutics, 304, (2005), 63–71.

3. Murthy SN. AAPS Annual Meeting. Orlando, Florida, USA, 25-29 October 2015.

4.Shin et al. AAPS Annual Meeting. Orlando, Florida, USA, 25-29 October 2015

5. Roberts, MS. FDA workshop on Bioequivalence testing of Topical Drug Products. Silver Springs, Maryland, USA, 20 October 2017.

6. DÍEZ-Sales et al. Journal of Pharmaceutical Sciences, Vol. 94, No. 5, (2005), 1039-1047.

FUNDING

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.

aaps PharmSci 360

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PBPK model when adequately parametrized with regard to drug product quality attributes can be used for "bottom-up" predictions of *in vitro* skin permeation of acyclovir

TABLE 1. FORMULATION RELATED MODEL INPUTS FOR ZOVIRAX® AND ACICLOSTAD® CREAMS (5% W/W)

Parameter(s)	Zovirax®	Aciclostad®	Comment
Vehicle molar volume (mL/mol)	41.05	26.84	Calculated
Amount of drug product applied (mg/cm^2)	15	15	Murthy 2015[3]
Density of formulation (g/cm^3)	1.017	1.0155	Murthy 2015[3]
Volume of formulation (mL)	0.0147	0.0148	Murthy 2015[3]
Thickness of formulation (cm)	0.0147	0.0148	Murthy 2015[3]
Viscosity (cP)	8360	29300	Murthy 2015[3]
Volume of water phase (% v/v)	33	66	Roberts 2017[5]
Volume of PG (% v/v)	40	15	Trottet et al. 2005[2]
Volume of solid particle (% v/v)	4.14	4.12	Calc from dose applied
Volume of dispersed phase (% v/v)	22.86	14.88	Calc [100-(Vol of Water+PG+Solid Particle)]
pH of formulation after 2 h	7	6.2	Considering buffering effect of skin
Acyclovir amount dissolved in aqueous Phase (mg/g)	0.492	0.365	Murthy 2015[3]
Total acyclovir amount dissolved (mg/g)	1.354	1.339	Murthy 2015[3]
Acyclovir amount dissolved in dispersed Phase (mg/g)	0.862	0.974	Calc (Total Amount Dissolved- Amount Dissolved in Aqueous Phase)
Ratio of acyclovir in dispersed/aqueous Phase	1.752	2.668	Calc (Amount Dissolved in Dispersed Phase/ Amount Dissolved in Aqueous Phase)
Acyclovir solubility (mg/mL)	1.49	0.545	Assumed that the amount of drug determined by Murthy is in volume of water phase
Klipsc:vehicle (Effect of PG)	0.25	0.14	DÍEZ-Sales et al. 2005[6]
Ksebum:vehicle (Effect of PG)	0.1017	0.0678	DÍEZ-Sales et al. 2005[6]
Evaporation profile	User input profile	User input profile	Murthy 2015[3]
Precipitation model	Growth Model	Growth Model	As implemented in Simcyp® Simulator V19

Calc: calculated, Vol: volume

CONTACT INFORMATION: sumit.arora@certara.com

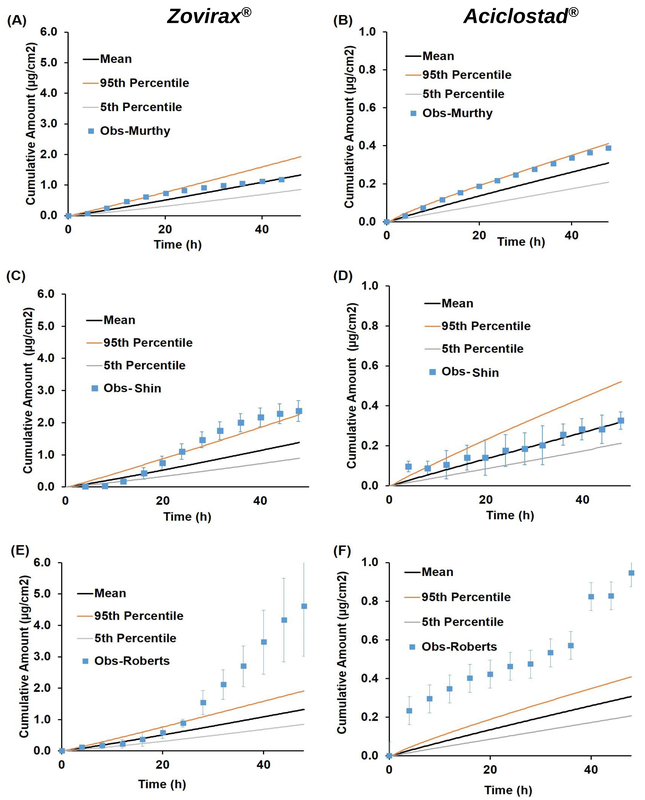

FIGURE 1. OBSERVED AND PREDICTED CUMULATIVE AMOUNT (MG/CM^2) OF ACYCLOVIR IN RECEPTOR FLUID OVER TIME FROM TOPICAL APPLICATION OF 15 MG/CM^2 OF ZOVIRAX® (A, C, E) AND ACICLOSTAD® (B, D, F) CREAM. SQUARES REPRESENT THE OBSERVED DATA REPORTED BY MURTHY 2015[3] (MEAN, N = 6), SHIN ET AL. 2015[4] (MEAN ± SE, N = 6) AND ROBERTS 2017[5](MEAN ± SD, N = 6).

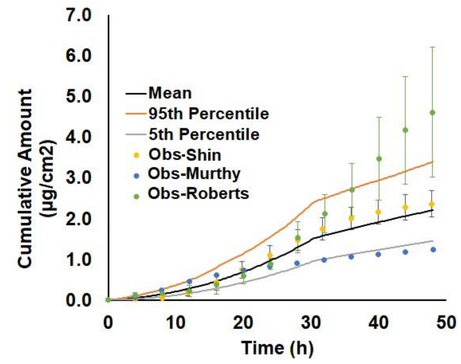

FIGURE 2. OBSERVED AND PREDICTED CUMULATIVE AMOUNT (MG/CM^2) OF ACYCLOVIR IN RECEPTOR FLUID OVER TIME FROM TOPICAL APPLICATION OF 15 MG/CM^2 OF ZOVIRAX® WITH TIME-DEPENDENT STRATUM CORNEUM LIPID:VEHICLE PARTITION COEFFICIENT CONSIDERING THE EFFECT OF PROPYLENE GLYCOL ON ACYCLOVIR PENETRATION THROUGH THE SKIN. CIRCLES REPRESENT THE OBSERVED DATA REPORTED BY MURTHY 2015[3] (MEAN), SHIN ET AL. 2015[4] (MEAN ± SE, N = 6) AND ROBERTS 2017[5] (MEAN ± SD, N = 6).