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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Poster Number: 296
CRS Virtual Annual Meeting
June 29 – July 2, 2020

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Disclaimer

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 presentation 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.

Outline of the Presentation

1) Background and aim of the research
2) Model structure and input parameters
3) PBPK modeling plan for Zovirax® Cream, 5%
4) Results
5) Conclusions

Background of the Research

- 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as part of an *in vitro* characterization-based approach for establishing bioequivalence (BE) in the published FDA Draft Guidance on Acyclovir (Topical cream, 5%).[1]

- A verified physiologically based pharmacokinetic (PBPK) model of *in vitro* skin permeation (IVPT) experiment can enhance our understanding of how drug product quality attributes can influence skin permeation of the applied drug substance.

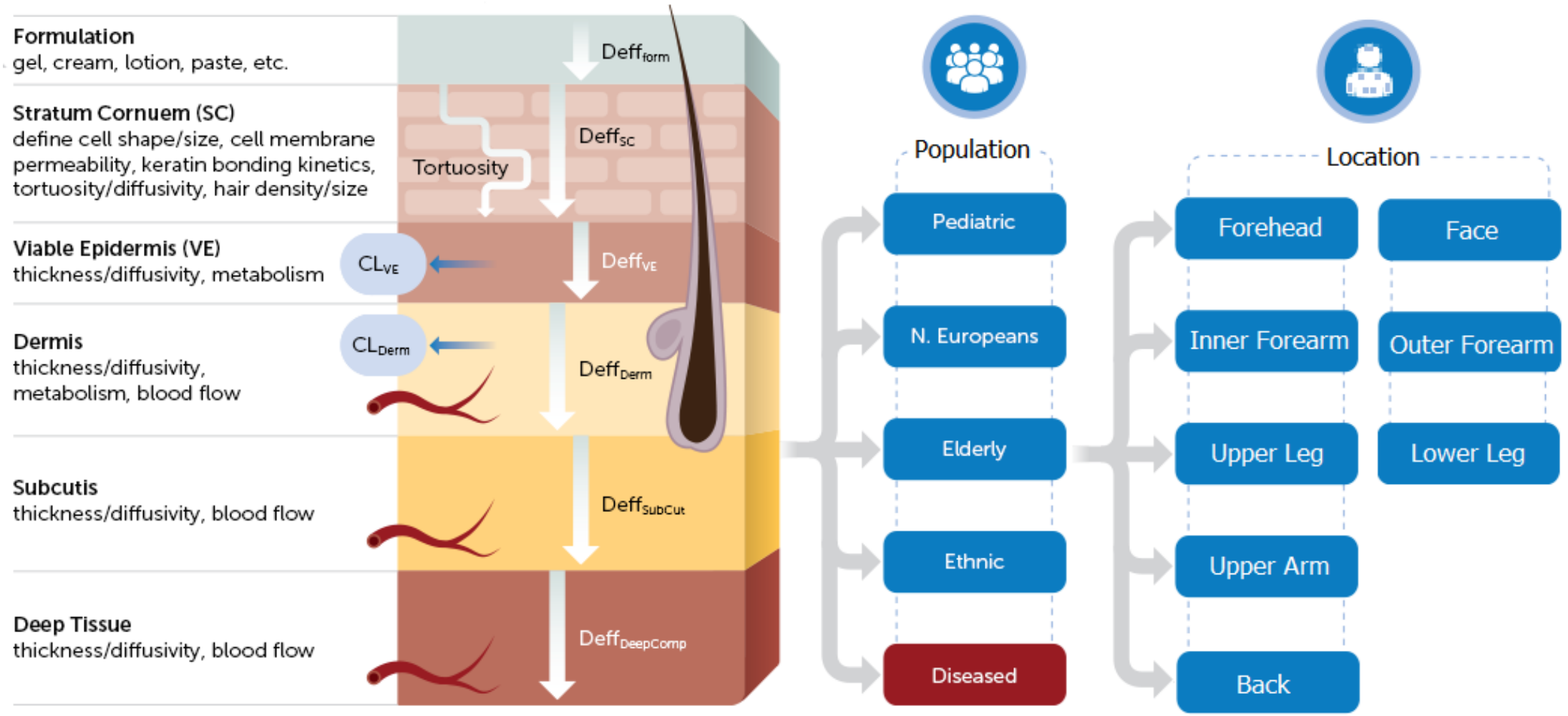
- These PBPK models can also be utilized to understand the interplay between the drug substance and key inactive ingredient(s) in influencing skin permeation of the drug substance.

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 Draft Guidance on Acyclovir (Topical Cream, 5%) 2016.

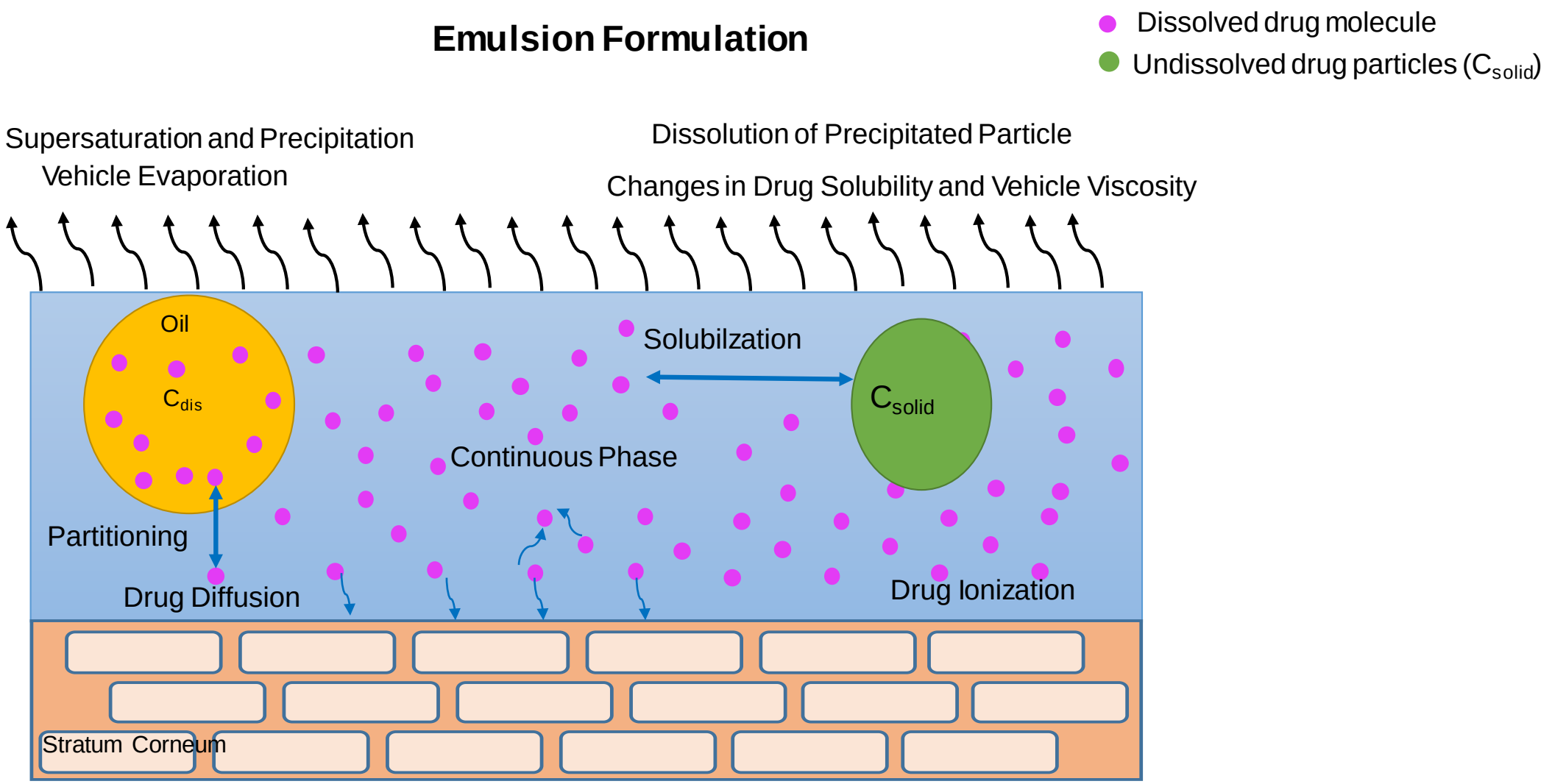
Aim of the Current Research

The present study aimed to develop a mechanistic “bottom-up” PBPK model integrating drug product quality attributes to predict *in vitro* permeation of acyclovir from acyclovir commercial cream, Zovirax® (acyclovir) Topical 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.

Simcyp's Multi-Phase Multi-Layer (MPML) MechDermA Model



Modeling Zovirax® Cream, 5% – Metamorphosis of topical formulations



Simple topical formulations are not that ‘simple’ to model

Input Parameters Needed to Parameterize the PBPK Model

Systems Data | **Trial Design** | **Drug Data** | **Formulation**

Systems Parameters

In vitro Simulation

- Type of skin sample
- Thickness of skin sample
- Active diffusion area
- Volume of receptor fluid
- Skin physiology (database generated from meta-analysis, can be modified by the user)

Trial Design

- Number of subjects
- Demographics (donor age range, gender)
- Dose
- Area of Application
- Duration of simulation

Drug Parameters

- MW
- LogP
- pKa

Skin Model Inputs (Partition and Diffusion Coefficient)

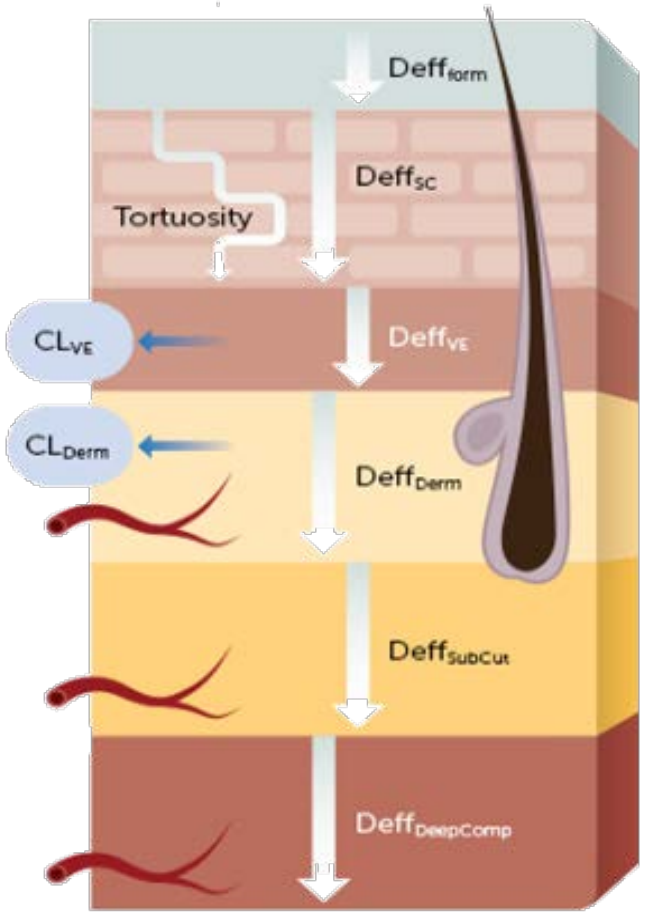
- $Kp_{SClipids:Water}$ (QSAR)
- $Kp_{SC:VE}$ (QSAR)
- $Kp_{Dermis:VE}$ (QSAR)
- $Kp_{Dermis:Blood}$ (QSAR)
- D_{SClip} (QSAR)
- D_{VE} (QSAR)
- D_{Dermis} (QSAR)
- fu_{SC} (QSAR)

Formulation Data

- Composition
- Drug solubility in different phases
- Drying rate (weight loss)
- Specific gravity
- Particle size (solid particles/droplets)
- Rheology (viscosity)
- Drug precipitation

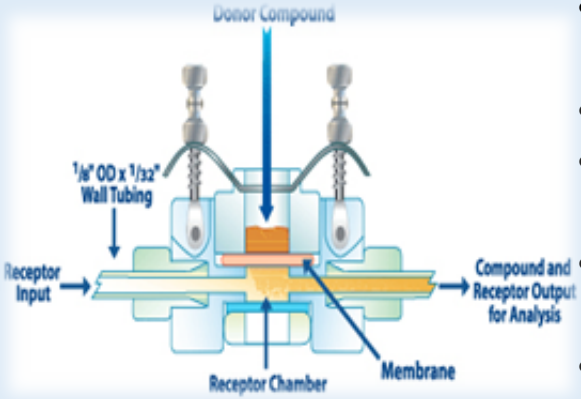
Kp – Partition Coefficient
D – Diffusion Coefficient

Setting the *In vitro* Skin Permeation Setup using MPML MechDermA Model



MPML MechDermA Model

‘Flow Through’ Cell Setup Parameters



- Select relevant skin physiology (skin site - back was used in the present case)
- Adjust skin layer thickness (dermatomed skin)
- Set subcutis (for dermatomed skin) as receptor chamber and match receptor chamber volume
- Set systemic elimination to ‘zero’ (such that the drug will accumulate in the systemic compartment)
- Set blood flow scalars to match experimental flow rate

PBPK Modelling Plan of Zovirax Cream

Two modeling approaches were explored to understand the effect of propylene glycol (PG) in influencing acyclovir skin permeation

Static Approach

- 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 was considered

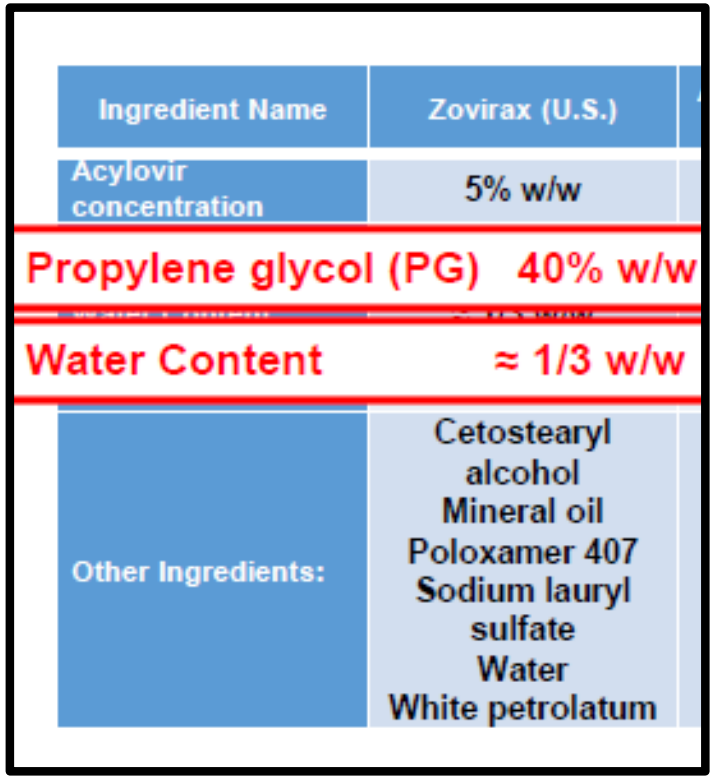
Dynamic Approach

- Time-dependent increase in $Kp_{sc\ lipids:vehicle}$ as the result of the hypothesized skin permeation of PG was considered

Composition of Zovirax Cream

Zovirax Cream (Approved in US)

	Zovirax US
Components	%(w/w)
Water	33
Propylene Glycol	40[a]
Solid Particle	4.14[c]
Dispersed phase	22.86[d]



Ingredient Name	Zovirax (U.S.)
Acylovir concentration	5% w/w
Propylene glycol (PG)	40% w/w
Water Content	≈ 1/3 w/w
Other Ingredients:	Cetostearyl alcohol Mineral oil Poloxamer 407 Sodium lauryl sulfate Water White petrolatum

Taken From Prof. Mike Roberts Presentation at US FDA[b]

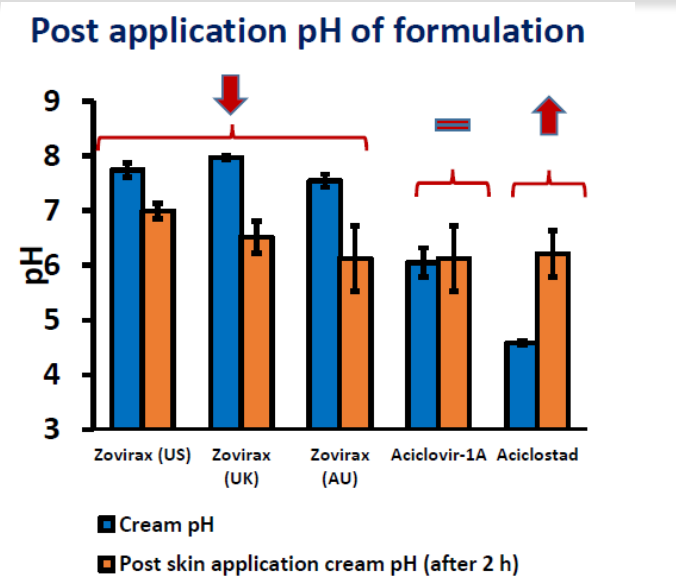
Information we have regarding composition of Zovirax Cream

[a]Trottet et al., International Journal of Pharmaceutics, 304, (2005), 63–71, [b]Roberts, MS. FDA workshop on Bioequivalence testing of Topical Drug Products, Silver Spring, Maryland, USA, 20 October 2017, [c]Calculated from dose applied, [d]Calculated [100-(Vol of Water+PG+Solid Particle)]

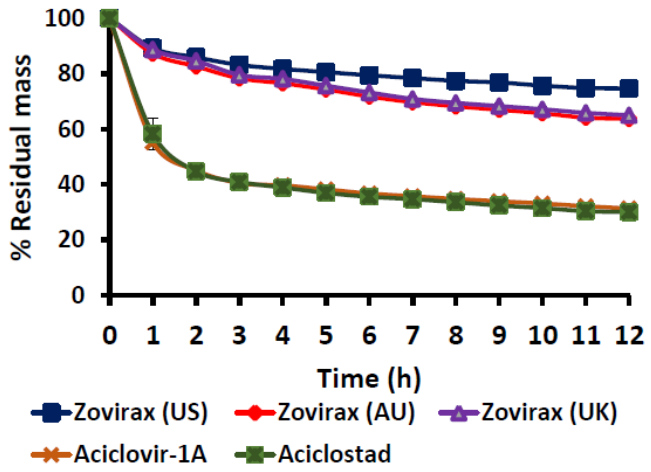
Structural and Physical Characterization of Zovirax Cream

Key input model parameters such as those related to physical and structural characterization of the Zovirax® Cream, 5% (Table below) were obtained from Murthy 2015.

Parameter	Zovirax US %(w/w)
Volume of Formulation (mL)	0.0147
Thickness of Formulation (cm)	0.0147
Viscosity (cP)	8360
pH of formulation after 2 h	7
Drug Solubility in Continuous Phase (mg/mL)	1.49
Ratio Dispersed/Aqueous Phase	1.752
Evaporation Profile	User Input Profile
Precipitation Model	Growth Model



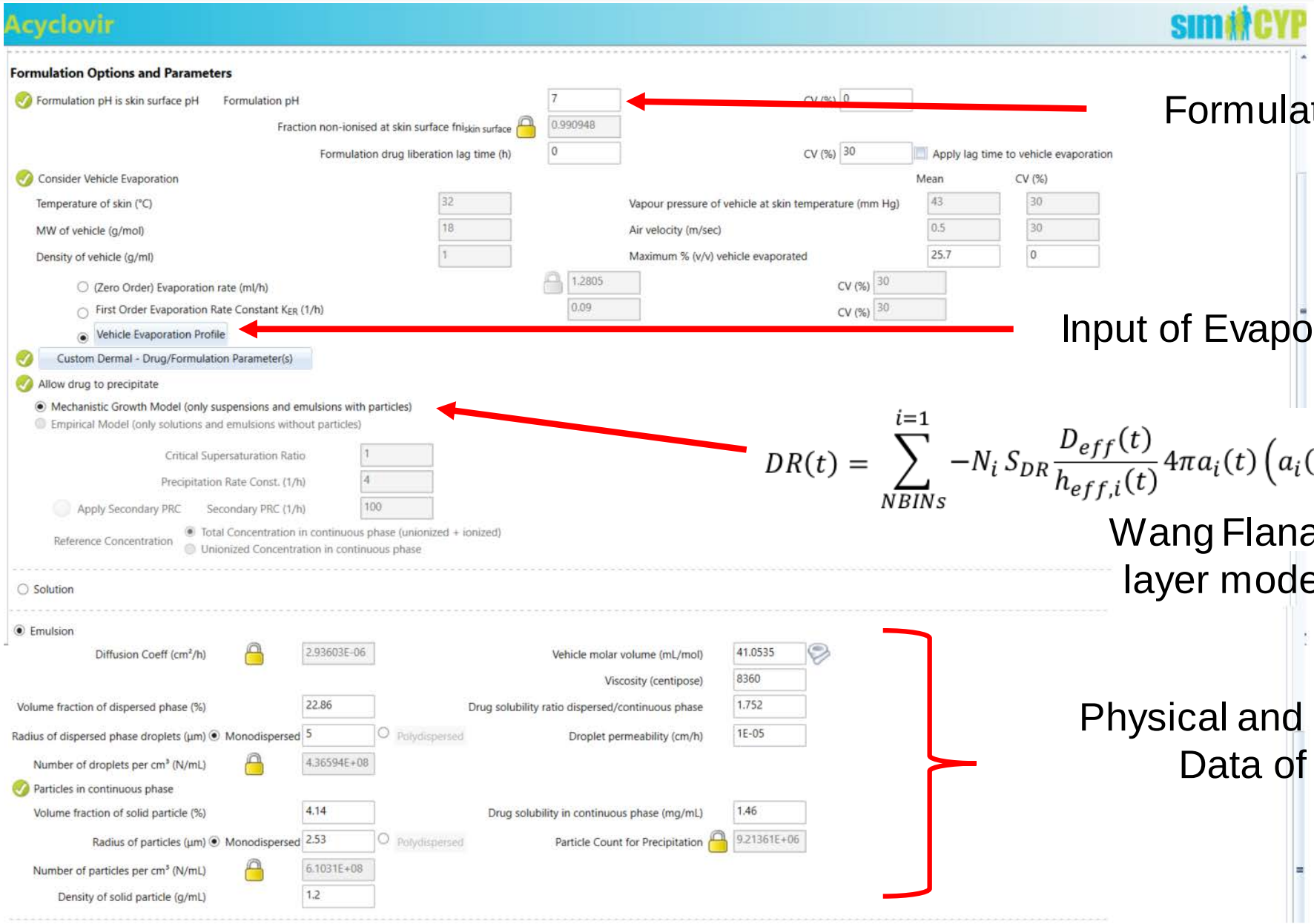
pH of formulation after application on skin



Evaporation profile of Acyclovir products

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

Parameterization of Formulation Parameters in MPML MechDermA Model



Formulation pH Input

Input of Evaporation Profile

$$DR(t) = \sum_{NBINs}^{i=1} -N_i \, S_{DR} \frac{D_{eff}(t)}{h_{eff,i}(t)} 4\pi a_i(t) \left(a_i(t) + h_{eff,i}(t)\right)\left(S_{surface}(t) - C_{bulk}(t)\right)$$

Wang Flanagan Equations (Diffusion layer model for particle dissolution)

Physical and Structural Characterization Data of Topical Formulations

Effect of Propylene glycol (permeation enhancer) on Acyclovir Skin Permeation

Table 2. ACV Skin Permeation Parameters from Solvent Systems and Carbopol® 971-P Gels at 0.5% (w/w), without and with 10%, 30%, 50%, and 70%, (w/w) PG: Partition (P') and Diffusion (D') Parameters*, Permeability Coefficients (K_p)*, Lag Time (t_L) and Enhancement Ratios (ER)

Vehicle	Partition Parameter (P')	Diffusion Parameter (D')	$K_p \times 10^4$ (cm/h)	Lag Time (t_L, h)	ER
Solvent system					
0	0.081 (0.024)	0.010 (0.002)	7.81 (1.36)	17	—
10	0.112 (0.019)	0.010 (0.001)[a]	11.43 (1.83)[a]	16	1.5
30	0.201 (0.039)	0.011 (0.002)[a]	21.15 (4.02)[b]	16	2.7
50	0.529 (0.060)	0.012 (0.001)[a]	63.59 (7.63)[b]	14	8.1
70	0.632 (0.142)	0.013 (0.002)[a]	78.97 (15.71)[b]	13	10.1
Hydrogels					
0	0.023 (0.005)	0.008 (0.001)	1.79 (0.48)	21	—
10	0.044 (0.011)	0.007 (0.001)[a]	3.10 (0.35)[a]	24	1.7
30	0.050 (0.013)	0.008 (0.002)[a]	4.10 (1.04)[a]	20	2.3
50	0.108 (0.012)	0.011 (0.001)[a]	12.10 (1.38)[b]	15	6.8
70	0.111 (0.034)	0.009 (0.002)[a]	9.99 (4.12)[b]	19	5.6

*The data are the mean of three determinations. Standard deviations are indicated in parenthesis.
[a]Non-significant differences with respect to 0% PG (Tukey test, $\alpha = 0.05$).
[b]Significant differences with respect to 0% PG (Tukey test, $\alpha = 0.05$).

Calculation of Scalar for Klipsc:veh

%PG	Partition Parameter (P)
0	0.081
30	0.201
50	0.529
40	0.365
Scalar	4.5

Proposed mechanism: propylene glycol increases the partitioning of acyclovir from the drug product to the stratum corneum

DI´EZ-Sales et al., Journal of Pharmaceutical Sciences, Vol. 94, No. 5, (2005), 1039-1047

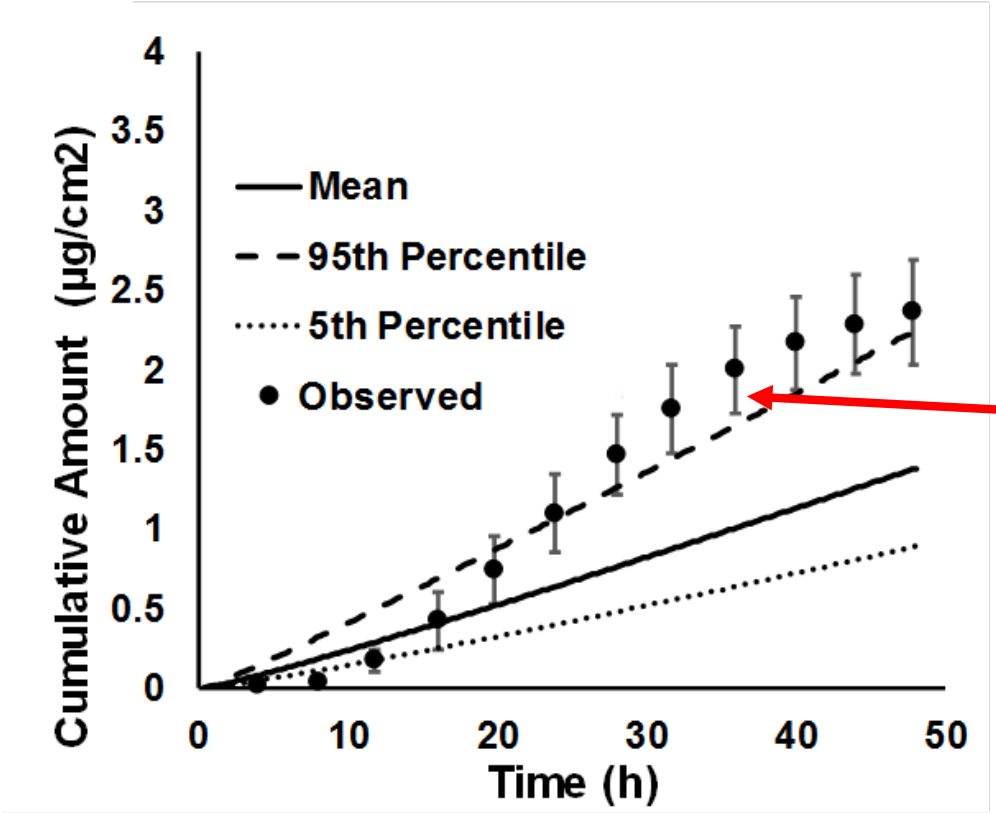
Partition and Diffusion Parameters of Acyclovir across various skin layers

Parameter	Value	Unit of measure	Method
$Kp_{sc\ lipids:vehicle}$	0.117	NA	Hansen 2013
$K_{lip/v}$	0.25	NA	Calc (DI´EZ-Sales et al. 2005)
$Kp_{sebum/water}$	0.048	NA	Calc
$K_{sebum/v}$	0.101	NA	Calc (DI´EZ-Sales et al. 2005)
$Kp_{SC/VE}$ (forearm)	0.90	NA	Shatkin and Brown QSAR
$Kp_{Dermis/VE}$	0.765	NA	Modified Chen 2015
$Kp_{Receptor:Dermis}$	1	NA	Assumed
$P_{corneocyte}$	4.5E-05	cm/h	Assumed and Scalar Applied
Dsclip	5.9E-04	cm^2/h	Johnson QSAR
Tortousity	2112.02	NA	Johnson QSAR
D_{Dermis}	0.00778	cm^2/h	Modified Chen 2015
D_{ve}	0.00778	cm^2/h	Modified Chen 2015
$D_{subcutis}$	0.00072	cm^2/h	Johnson 1996
Fraction unbound in SC	0.194		Polak et al. 2016

Parameters in red includes the effect of propylene glycol on Acyclovir Permeation

IVPT Simulation – Simulation of 'Flow Through' Diffusion Cell 'Static Approach'

Simulations were carried out with 15 mg/cm^2 of formulation applied on a 1 cm^2 diffusional surface area. All simulations results are mean of 10 trials of 6 virtual donors (healthy volunteers, forearm as application site). Observed data (Mean ± SE, n = 6) was obtained from Shin et al. 2015.



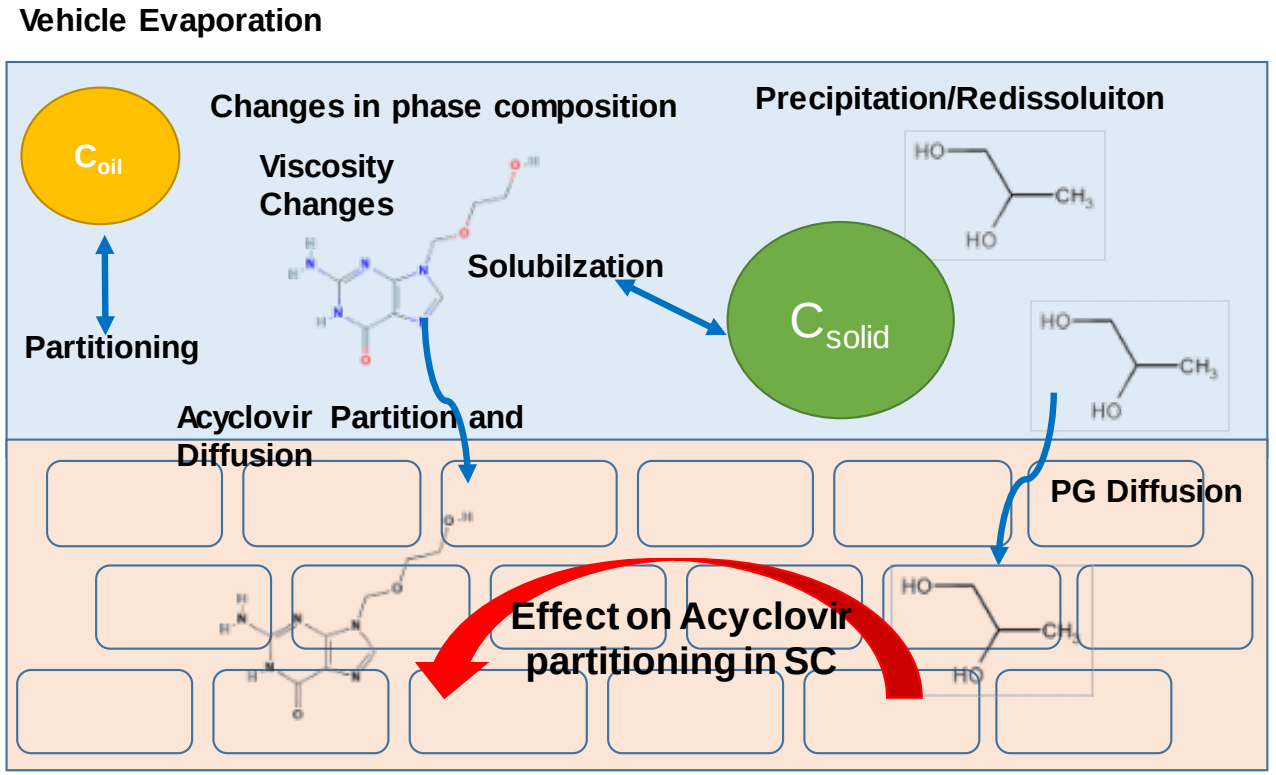
S-Shaped Curve

With 'Static Approach' the model was able to capture the extent of acyclovir permeation however the shape of the profile was not adequately captured

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

Semi-Mechanistic Modeling of Effect of Propylene Glycol on Acyclovir Permeation

Dynamic Process Happening During Product Metamorphosis



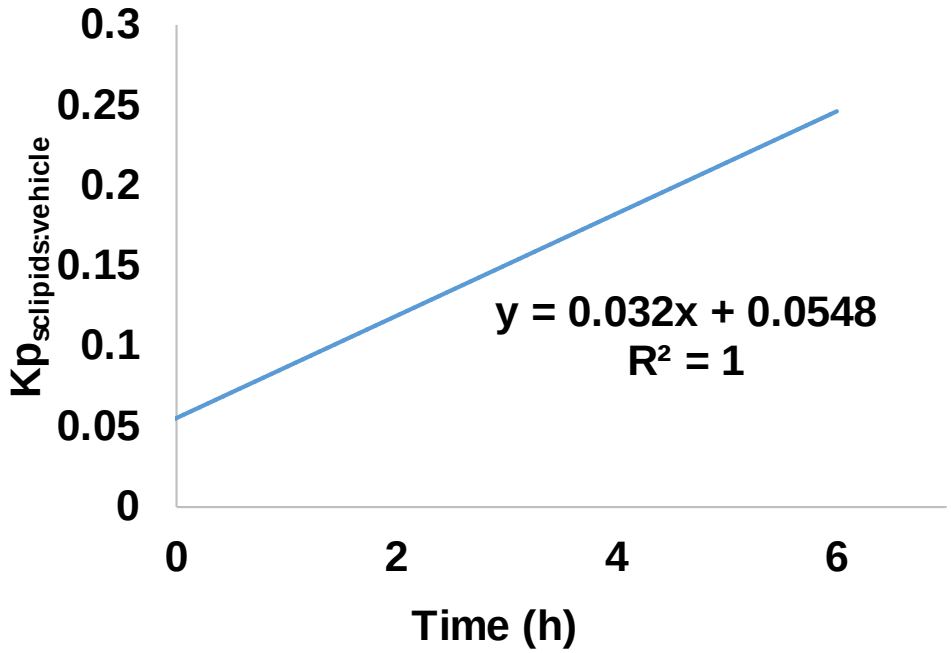
Hypothesis: Propylene Glycol increases the partitioning of acyclovir from the drug product in the stratum corneum

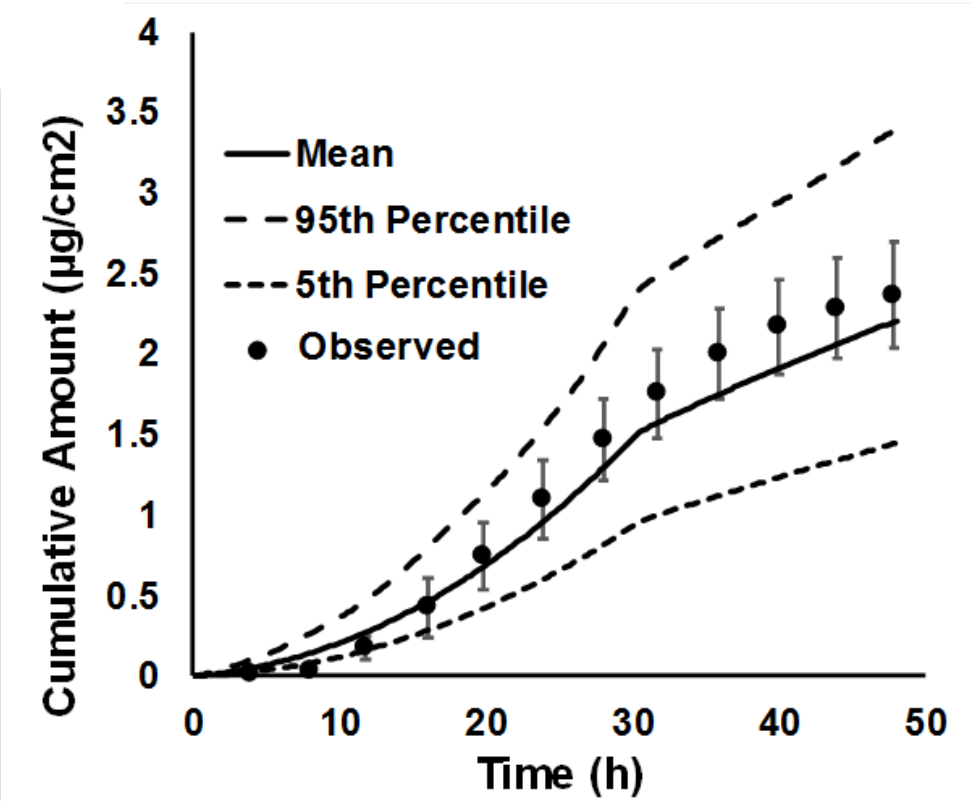
DI´EZ-Sales et al., Journal of Pharmaceutical Sciences, Vol. 94, No. 5, (2005), 1039-1047; Roberts et al., ASCPT Annual Meeting, 2019.

IVPT Simulation – Simulation of 'Flow Through' Diffusion Cell 'Dynamic Approach'

A time dependent linear increase in the $Kp_{sc\ lipids:vehicle}$ was considered for 30 hours owing to the hypothesized PG skin permeation

Initial Point	$Kp_{sc\ lipids:vehicle}$	Comment
0	0.055	Calculated
6	0.25	Calculated

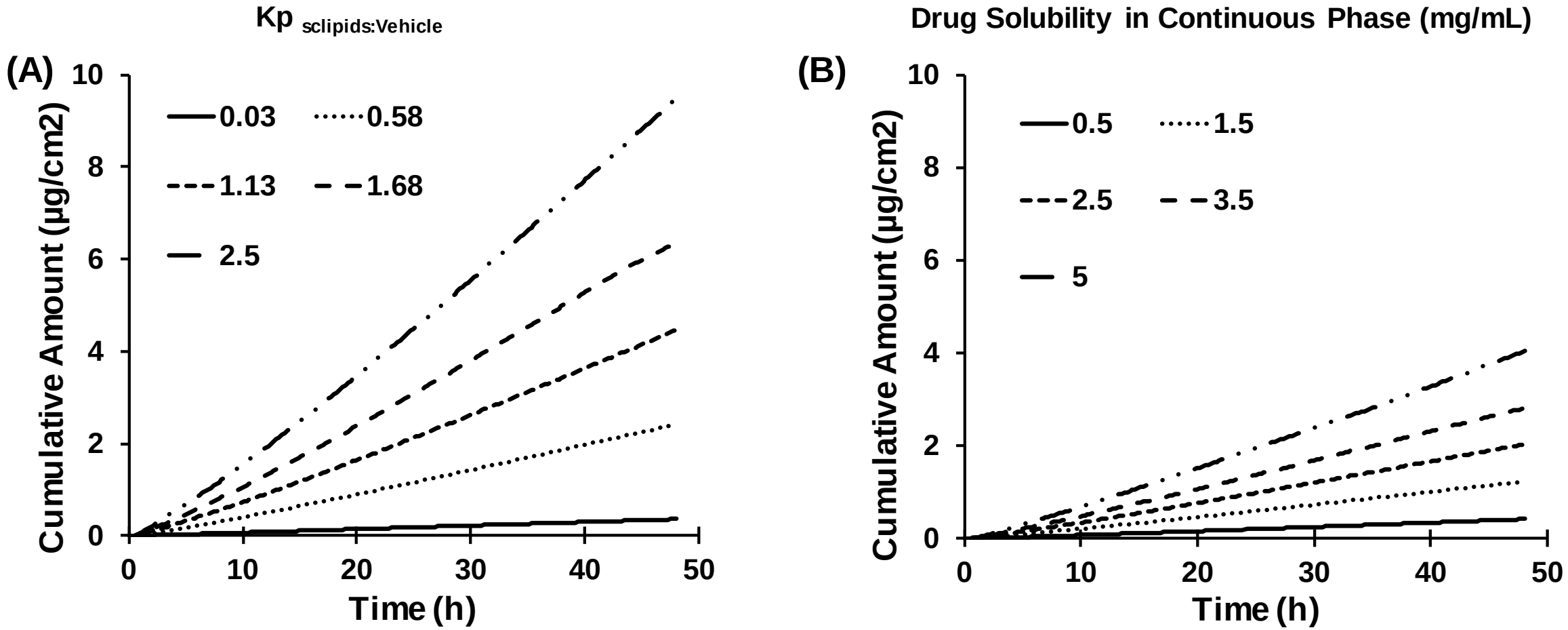




'Dynamic Approach' was able to capture both the rate and extent of *in vitro* acyclovir skin permeation from Zovirax Cream

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

Sensitivity Analysis



Sensitivity analysis of the impact of the formulation to stratum corneum lipids ($Kp_{sc\ lipids:vehicle}$) 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. $Kp_{sc\ lipids:vehicle}$ was 0.25 and acyclovir solubility was 1.49 mg/mL in the final model.

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.

Acknowledgments and Funding

Simcyp

- James Clarke
- Farzaneh Salem
- Tariq Abdulla
- Arran Hodgkinson
- Santosh Kumar Puttrevu
- Krishna Chaitanya Telaprolu
- Susan Burkhill

US FDA

Sam Raney

Markham Luke

Andrew Babiskin

Liang Zhao

Lei K Zhang

Funding: US FDA Grant 1U01FD005225 and 1U01FD006522

Please feel free to send your questions at the following email address:

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Questions?