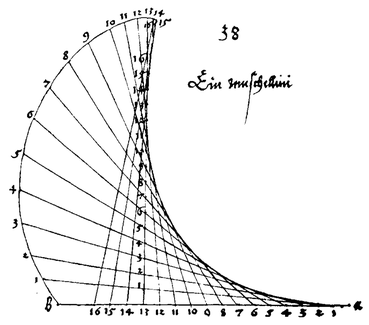
In-Silico Investigation of the Cutaneous Pharmacokinetics of Acyclovir from Creams Containing Acyclovir and a Penetration Enhancer

Rebecca Wittum[1], Junxi Wang[1], Yousuf Mohammed[2], Sarika Namjoshi[2], Jeffrey Grice[2], Priyanka Ghosh[3], Sam G. Raney[3], Michael Roberts[2,4], Arne Nägel[1], Gabriel Wittum[1,5]

1 Goethe-Center for Scientific Computing, Goethe Universität Frankfurt am Main
2 Therapeutics Research Centre, Diamantina Institute, University of Queensland, Brisbane
3 Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, U.S. FDA, Silver Spring, MD
4 School of Pharmacy and Medical Sciences, University of South Australia, Adelaide
5 Computer, Electrical and Mathematical Sciences and Engineering, King Abdullah University of Science and Technology, Thuwal
Contact: rebecca.wittum@gcsc.uni-frankfurt.de



Abstract

In this work, we combined experimental observations of topical drug delivery from acyclovir cream, 5% (Zovirax) with in-silico approaches to model these observations, in order to gain new insights into the potential factors influencing the cutaneous pharmacokinetics observed, and to thereby advance beyond phenomenological insights.

Experimental Data

In-vitro permeation tests were performed on heat separated epidermal membranes of abdominal human skin, obtained from three different skin donors with three replicates each. An acyclovir cream, 5% (Zovirax) containing water and propylene glycol, among other ingredients, was applied at 15 mg/cm^2 on an area of 1.33cm^2. The cumulative amount of acyclovir permeating through the skin into the receptor compartment of the diffusion cell was measured every four hours till the end of the experiment at 48 h. A review of the experimental results, including other acyclovir products for comparison, revealed that, in some cases, the formation of an intermediate plateau in the pharmacokinetic profile can be observed some hours after application. The available data suggested a possible dependence of this phenomenon on the propylene glycol content of the products studied. Results for the acyclovir cream, 5% (Zovirax), averaged over all nine replicates, are portrayed in figure 1.

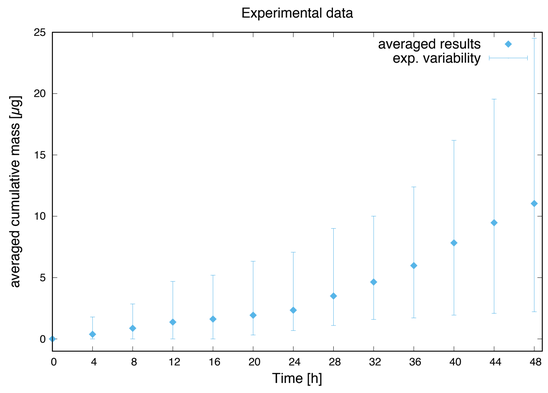


Figure 1: Experimental results for the averaged cumulative mass of acyclovir that penetrated the epidermal membranes.

In-Silico Approach

In order to investigate the interplay of acyclovir with the co-permeating propylene glycol, and the effect of product formulation on the cutaneous pharmacokinetic profiles, we developed an in-silico compartmental model of the skin, which includes excipient co-permeation and takes excipient interdependencies into account. In a qualitative concept study, using a macroscopic model with deposition, barrier and uptake layers, we identified possible mechanisms, like changes in thermodynamic or barrier properties, that could lead to an intermediate plateau in the cutaneous pharmacokinetic profile. A subsequently developed, quantitative model, consisting of formulation layer, stratum corneum, stratum granulosum and stratum spinosum, describes excipient transport through this model geometry, depending on local diffusion and partition coefficients:

$$\frac{\partial}{\partial t}K(x)u(x) + \nabla[-D(x)K(x)\nabla u(x)] = 0$$

$$K(x) = \begin{cases} K_{form}, x \in \text{Formulation layer} \\ \vdots \\ K_{spin}, x \in \text{Stratum spinosum} \end{cases} \qquad D(x) = \begin{cases} D_{form}, x \in \text{Formulation layer} \\ \vdots \\ D_{spin}, x \in \text{Stratum spinosum} \end{cases}$$

The expression $K(x)u(x)$ represents a substance's local concentration $C(x)$. To obtain substance and skin layer specific values of K and D, we determined model parameters for water, acyclovir and propylene glycol based on physicochemical parameters, e.g. [1]. The thickness H of each individual layer is taken from experimental measurements. The parameters used in this model are summarized in table 1.

		Water		Propylene gylcol		Acyclovir	
	H [μm]	K	D [$\mu m^2/s$]	K	D [$\mu m^2/s$]	K	D [$\mu m^2/s$]
Formulation	150	0.042	6.88	0.12	2.86	0.0275	1.729
S. corneum	13	0.183	0.001072	0.29	0.0001039	0.2439	$2.54\,10^{-7}$
S. granulosum	8	0.599	315.84	0.6	63.345	0.6	3.061
S. spinosum	22	0.599	381.14	0.6	107.18	0.6	46.825

Table 1: Model parameters for water, propylene glyocol and acyclovir at different sites.

Apart from the basic diffusion equation, which is defined for water, propylene glyocl and acyclovir, the model takes excipient interdependencies between acyclovir and the co-permeating water and propylene glycol into account. Both are known to affect the barrier properties of the stratum corneum and the effect of their presence on the penetration of acyclovir is modelled via a concentration-dependent diffusion coefficient

$$D^*_{SC,ACV} = D_{SC,ACV} + \alpha\, C_{SC,PG} + \beta\, C_{SC,H_2O}.$$

The parameters α and β determine the extent of a lowered stratum corneum barrier, dependent on the local amount of propylene glycol and water, respectively. Additionally evaporation of water from the formulation surface is included via

$$-D_{don,H_2O}\nabla u_{H_2O}(x)\vec{n} = \omega\, u_{H_2O}(x).$$

This equation describes the concentration-dependent loss of water from the formulation across the its surface with a proportionality constant ω.

Simulation concept

The parameters α, β and ω have, as yet, no experimental or theoretical estimates available and are therefore considered fitting parameters. At the start of every simulation a finite amount of water, propylene glycol and acyclovir of two representative formulations, is homogeneously distributed in the formulation layer. Due to acyclovir's limited solubility only 10% is considered eligible for transport. With this setup the possibilty of penetration enhancement and evaporation as cause for the observed acyclovir penetration profiles is investigated.

Results

Choosing $\alpha = \beta = \omega = 0$ reduces the developed model to its basic diffussion equations without enhancement or water evaporation, and due to acyclovir's extremely small diffusion coefficient in the stratum corneum, the simulation severly underpredicts the experimental results. Introducing $\alpha \neq 0$ causes an increase in penetrated acyclovir starting at about 20 hours after application, which is dependent on the propylene glycol content of the simulated product. Assuming $\beta \neq 0$ instead, results in an earlier rise of the penetration profile, in this case dependent on the water content:

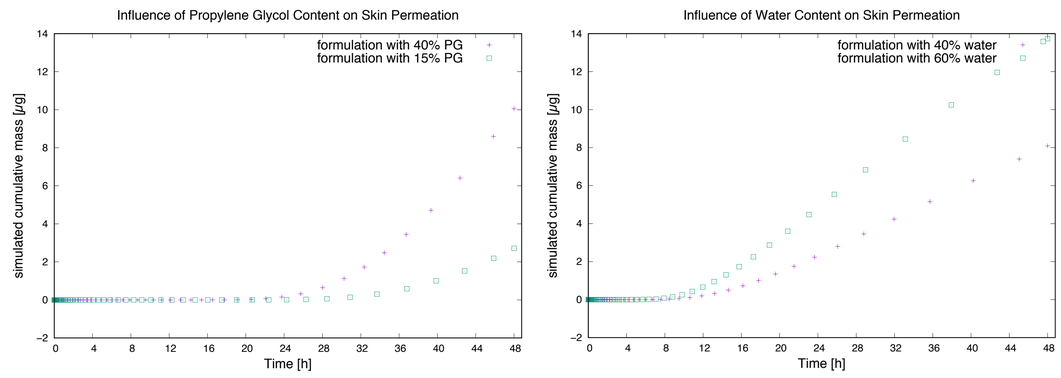


Figure 2: Simulated acyclovir penetration profiles with enhancement by propylene glycol (left) or water (right).

Adding water evaporation $\omega \neq 0$ from the formulation surface to the case with $\beta \neq 0$ leads to a levelling off in the simulated penetration profile, some hours after application. Assigning non-zero values to all three parameters α, β and ω can result in penetration profiles that form an intermediate plateau, similar to what was observed in the experimental data:

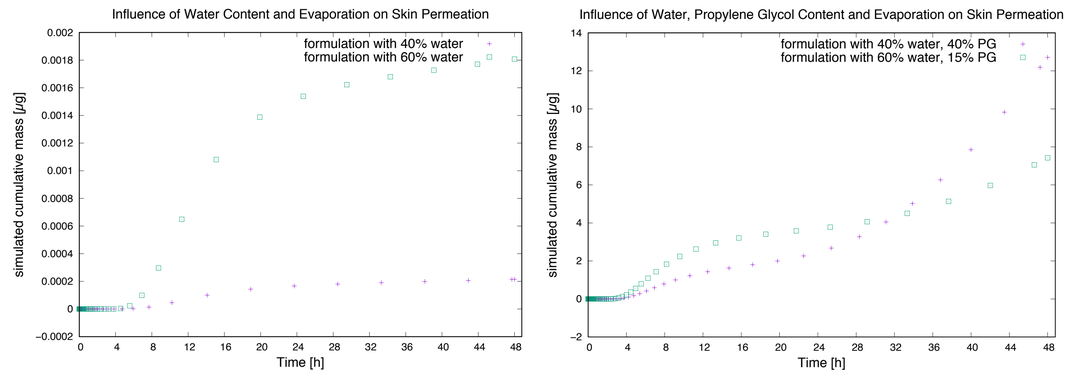


Figure 3: Simulated profiles with evaporation and enhancement by only water (left) or water and propylene glyocl (right).

Substituting the values for water and propylene glycol from those empirically characterized and estimated for acyclovir cream, 5% (Zovirax) to those similarly estimated for other acyclovir cream, 5% products, a good approximation of the experimental data was achieved by using $\alpha = 0.00003\,\mu m^2/s \cdot \mu m^3/\mu g$, $\beta = 0.000043\,\mu m^2/s \cdot \mu m^3/\mu g$ and $\omega = 0.02\,\mu m/s$:

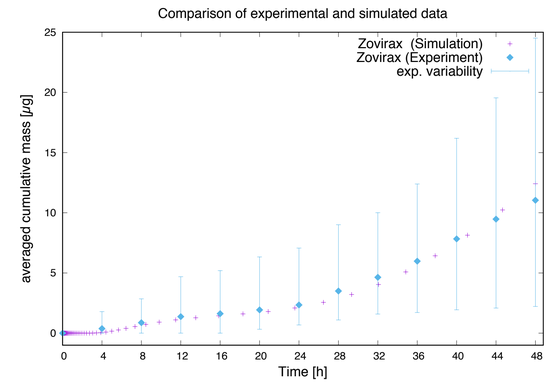


Figure 4: Simulated and experimental penetration profiles for acyclovir.

Conclusions

Our in-silico investigation of acyclovir creams suggests that penetration enhancement of acyclovir, due to the co-permeating water and propylene glycol, as well as evaporation of water from the formulation surface, might be responsible for the experimentally observed penetration profiles.

Ongoing Research

- Sensitivity analysis for parameters
- Experimental verfication of postulated effects
- Modelling solubility in the formulation layer

Acknowledgment

Funding for this project was made possible, in part, by the Food and Drug Administration through grant U01FD005232. Views expressed in this poster do not reflect official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

References

[1] R. Wittum, "Modeling diffusion through cellular membranes," Master's thesis, Karlsruhe Institute of Technology, 2016. [in German].

Goethe-Center for Scientific Computing