Development of an *in silico* model of topical acyclovir to explore formulation design

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PURPOSE

Acyclovir (ACY) creams are used for local treatment of HSV-1 infections in the basal epidermis. Local delivery to the skin through the stratum corneum (SC) must be effective to reach target concentrations deeper in the skin. Zovirax® cream has a high percentage of undissolved acyclovir and low dermal delivery, suggesting that ACY content may be reduced without affecting delivery to the skin. The Transdermal Compartmental Absorption and Transit™ (TCAT) model in GastroPlus® is a physiologically based mathematical model that simulates the dermal and systemic pharmacokinetics of topically applied compounds. A validated TCAT model of ACY can be used to investigate formulation properties of Zovirax cream and optimize design.

OBJECTIVE

Use the TCAT model in GastroPlus to demonstrate how a validated model of acyclovir dermal delivery can be used to explore the effect of decreasing ACY content in a topically applied cream.

METHODS

- Use composition and *in vitro* data to develop a model of ACY dermal delivery from Zovirax® cream 5% in GastroPlus 9.8.3
- Validate the model using *in vivo* tape stripping data
- Perform parameter sensitivity analysis on ACY content of the cream

RESULTS

TCAT ACY model parameters were developed based on measurements from the literature (Table 1). The model showed good agreement with tape-stripping data 6h and 23h after *in vivo* application of Zovirax cream (Figure 1). Model simulations were then performed where ACY content was reduced from the amount in Zovirax cream (Figure 2). No difference in the delivery to SC was predicted up to a 95% reduction in dose. Dermal delivery can be maintained across a wide dose range because undissolved ACY content is reduced while dissolved ACY concentration in the cream remains at saturation throughout the course of delivery (Figure 3).

Table 1. Summary of TCAT model parameters.

Parameter	Value	Units	Source / Derivation
ACY content	50	mg/g cream	Zovirax US prescribing information (2014)
θ^{disp}	0.282		Calculated from the composition[A]
Cont phase solubility	2.88	mg/mL	Diez-Sales et al. J Pharm Sci 94, 1039–1047 (2005).
Cont phase/water partition coeff, $K^{cont,w}$	2.62		Ratio of continuous phase and water solubilities
Disp phase/water partition coeff, $K^{disp,w}$	3.98E-02		Calculated from ADMET Predictor 10.3 Log $K_{o,w}$*
Effective diffusivity in continuous phase, D^{eff}	3.41E-08	cm²/s	Higuchi analysis of SN Murthy's in vitro release data[B,C]
Diffusivity in the dispersed phase, D^{disp}	1.11E-08	"	Extrapolated from ferrocene cyclic voltammetry data[D]
Dispersed phase droplet radius, r^{disp}	1	µm	A nominal value for emulsions
ACY particle radius	1.88	µm	One half d_{50} from SN Murthy's particle size data (d_{10} = 2.07 mm, d_{90} = 19 mm)[B]
SC permeability, P^{SC}	5.37E-09	cm/s	Robinson model (Wilschut et al, Chemosphere 30, 1275–1296 (1995).
VE permeability, P^{VE}	2.48E-04	"	Kretsos et al. Int J Pharm 346, 64–79 (2008).
Dermis permeability, P^{De}	2.85E-05	"	"
Sebum / hair permeability, P^{Sebum}	8.865e-10	"	$D^{Sebum} = D^{disp}$, $K^{Sebum,w}$ = 1.04e-2[H] with P^{Sebum} calculated via GastroPlus 9.8.3
Fraction bound in SC	0.215		Equilibrium keratin binding model[E,F,G]
Fraction bound to protein and lipid in VE & dermis	0.145		Bound fraction in skin (1 - $f_{u,skin}$), Lukačova Method, GastroPlus 9.8.3

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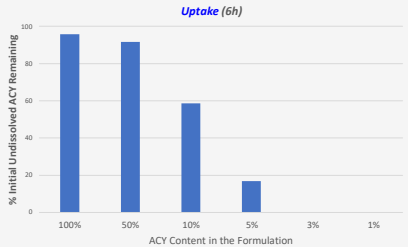

Figure 3. TCAT model predicted undissolved ACY content remaining in cream after 6-hour application

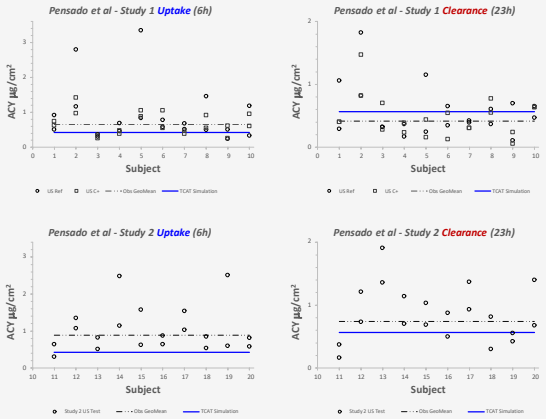

Figure 1. Total ACY concentrations (µg/cm²) in stratum corneum recovered via tape stripping on uptake at 6 hours (left) and clearance at 23 hours (right) of Study 1 (top, US Reference and US Comparator) and Study 2 (bottom, US Test) after *in vivo* application of Zovirax to the forearms (open symbols and geometric mean line in black), with TCAT model prediction (blue line).

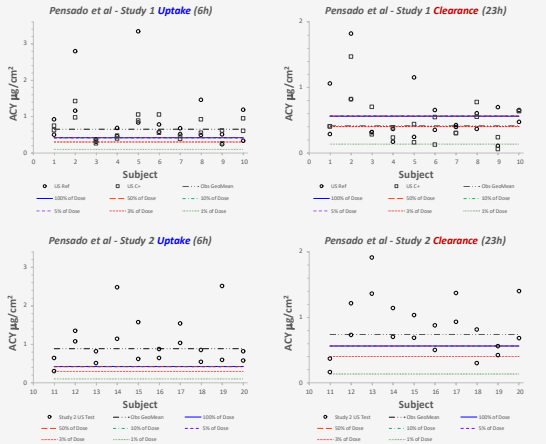

Figure 2. Total ACY concentrations (µg/cm²) in stratum corneum recovered via tape stripping on uptake at 6 hours (left) and clearance at 23 hours (right) of Study 1 (top, US Reference and US Comparator) and Study 2 (bottom, US Test) after *in vivo* application of Zovirax to the forearms (open symbols and geometric mean line in black), with TCAT model predictions of SC uptake and clearance at 100%, 50%, 10%, 5%, 3%, and 1% of Zovirax ACY content.

CONCLUSION

In vitro and *in vivo* experimental data can be used to build a validated TCAT model of skin permeation of acyclovir. The validated model can be used to explore formulation characteristics such as ACY content. Due to the high percentage of undissolved ACY in Zovirax cream, the model predicts that the same dermal delivery can be achieved with much lower ACY content.

REFERENCE

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ACKNOWLEDGMENT

Funding for this project was made possible, in part, by the US FDA through grants 1U01FD006526-01 and 1U01FD007320-01. Views expressed here do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices or organizations imply endorsement by the United States Government.

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