Advancements in the Dermal Physiologically-based Pharmacokinetic (PBPK) Modeling under the Generics Drug User Fee Amendments (GDUFA) Program

Eleftheria Tsakalozou, Zhanglin Ni, Andrew Babiskin, Liang Zhao

Office of Research and Standards, Office of Generic Drugs, Center of Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993

Background

Dermal physiologically-based pharmacokinetic (PBPK) modeling is a "bottom up" approach to quantitatively describe skin absorption of drug substances administered in transdermal delivery systems (TDS) or semisolid dosage forms accounting for formulation attributes impacting bioavailability. Under the GDUFA regulatory science program[1], research on dermatological product characterization/performance and enhancements on quantitative tools has been conducted since 2014. These published outcomes were leveraged to develop dermal PBPK models for various dermatological products.

Purpose

Develop and verify dermal PBPK models for the Reference Listed Drugs for the nicotine TDS[2], the lidocaine 2.5%/prilocaine 2.5% topical cream[3] and the acyclovir topical cream, 5%[4] that can be used to:

- Predict systemic and local (dermis) exposure to the drug substance following a single application of these three dermatological products.
- Assess the performance of the modeling software package utilized for the development of the previously mentioned dermal PBPK models under Grant #1U01FD005225 of the GDUFA regulatory science program (Office of Generic Drugs).[1]

Methods

The Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MPML-MechDermA) module built within the Simcyp® Simulator (Certara, Princeton, NJ) was used to describe absorption through the skin for three dermatological products. Dermis volume was estimated taking into account the application area and the dermis thickness and was further utilized in calculating the drug substance concentration in the dermis. Skin absorption parameters were modified from the default ones in the nicotine and lidocaine dermal PBPK models to better describe systemic exposure (clinical pharmacokinetic, PK, profiles) in healthy subjects or patients. Software default skin absorption parameters were utilized for the development of the acyclovir dermal PBPK model due to lack of systemic exposure data for this drug product. The PBPK models were initially developed (and verified) to describe systemic exposure following intravenous administration of the drug substance of interest. When application of dermatological drug products resulted in detectable blood concentrations for the drug substances of interest and the information was publicly available, a second verification step was performed.

Table 1: Summary of parameters utilized for model development.

	Nicotine TDS[2,*]	Ref	Lidocaine topical cream[#,3]	Ref	Acyclovir topical cream[4]	Ref
Physicochemical properties of drug substance						
MW	162.23	5	234.34	5	225.2	5
LogP	0.87	5	2.44	5	-1.56	5
pKa	monoprotic base, 8.86	5	monoprotic base, 8.01	5	2.27 and 9.25, ampholyte	5
B/P ratio	predicted		0.67	12	1	15
f_u	0.95	5	0.3	12	0.8	16
Systemic disposition model structure						
	Minimal PBPK Model		Minimal PBPK Model		Minimal PBPK Model	
Pharmacokinetic parameters						
V_{ss} (L/Kg)	3	6	1.5	5, 12	0.71	16
CL (L/h)	72	6	60	5, 12	19.62	16
Skin absorption						
$K_{p,\ SCLip:Vehicle}$	Hansen 2013	7	Hansen 2013	7	Hansen 2013	7
$K_{p,\ VE:SC}$	Shatkin & Brown	8	Shatkin & Brown	8	Modified Krestos 2008	17
$D_{SC,Lip}$	Wang 2006	9	Mitragotri 2003	13	Mitragotri 2003	13
D_{VE}	Bunge & Cleek	10	Bunge & Cleek	10	Krestos 2008	17
Keratin Binding	Dynamic absorption (predicted)		Steady State (predicted)		Steady State (predicted)	
Formulation options and parameters						
	Dermal patch, Controlled release	11	Emulsion (globule size, viscosity, drug solubility ratio)	14	Emulsion (globule size, viscosity, drug solubility ratio)	18
			Formulation pH 9.22	14	Formulation pH 7.74	18
			Vehicle evaporation (first order, K_{ER}=12 1/h)	14	Vehicle evaporation (first order, K_{ER}=0.02 1/h)	18

MW: molecular weight, B/P: blood to plasma, f_u: fraction unbound in plasma, V_{ss}: volume of distribution at steady state, CL: total clearance, K_p: partition coefficient, SCLip: stratum corneum lipid, VE: viable epidermis, D: Diffusion coefficient, K_{ER}: evaporation rate constant, Ref: reference. *The same set of parameters were used for model development under a previous software version. # The dermal PBPK model developed was for lidocaine and not prilocaine.

Results

Nicotine: predictions of systemic exposure described the observed PK profiles reasonably well and were improved compared to a previous version of the utilized software package

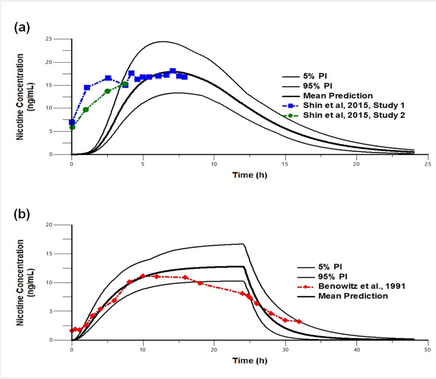

Figure 1: Predicted (mean, 5 and 95% PI, solid line) versus observed (mean, symbols) PK profiles of nicotine in plasma following application of the nicotine TDS in healthy volunteers. Simulated profiles were generated utilizing the developed dermal PBPK model (v17). Observed data were nicotine concentrations in the systemic circulation obtained in (a) healthy volunteers[11] and in (b) healthy smokers[19]. PI: Prediction Interval

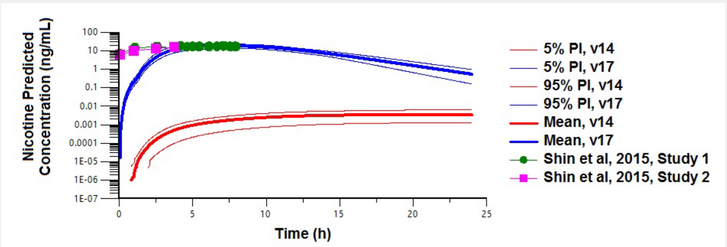

Figure 2: Predicted PK profiles (mean, 5 and 95% PI) of nicotine in plasma following application of the nicotine TDS in virtual healthy volunteers utilizing the dermal PBPK models developed in v17 (blue lines) and v14 (red lines). Observed data were nicotine concentrations in the systemic circulation obtained in healthy volunteers[11]. PI: Prediction Interval

Acyclovir: predictions of systemic exposure described observed PK profiles reasonably well while dermis concentrations were overpredicted

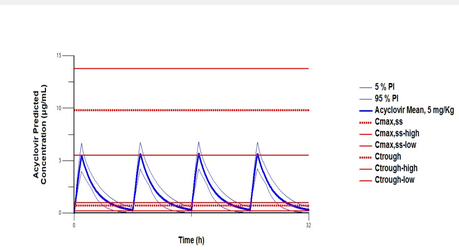

Figure 3: Predicted (mean, 5 and 95% PI, blue solid line) PK profiles of acyclovir in plasma following intravenous administration of acyclovir in adult patients[20] generated utilizing the developed PBPK model for acyclovir. Vertical red lines represent observed $C_{max,ss}$ (9.8 µg/mL, range 5.5 to 13.8) and observed C_{trough} (0.7 µg/mL, range 0.2 to 1.0). PI: Prediction Interval, Cmax: maximum concentration, SS: steady state, high-low: range provided

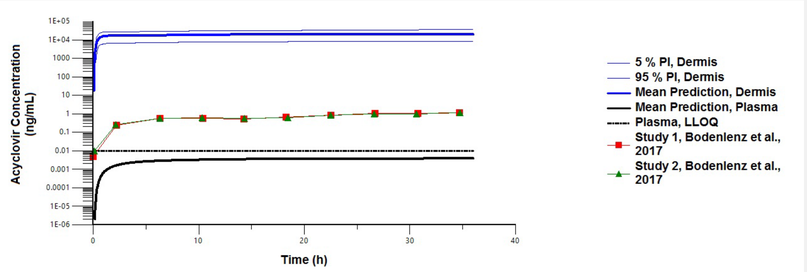

Figure 4: Predicted (mean, 5 and 95% PI, solid line) versus observed (mean, symbols) PK profiles of acyclovir in dermis collected with dermal open flow microperfusion following application of the acyclovir cream in healthy volunteers[21]. Simulated profiles in the plasma and dermis were generated utilizing the developed dermal PBPK model for acyclovir. Predicted plasma PK profiles (black solid line) remained below the reported in the literature LLOQ[4,21]. PI: Prediction Interval, LLOQ: Lowest Limit of Quantification

Lidocaine: predictions of systemic exposure described the observed PK profiles reasonably well while dermis concentrations were overpredicted

Table 2: Summary of observed and predicted PK parameters (and the predicted to observed PK parameter ratio) in male patients following the administration of the lidocaine topical cream[3]. Cmax: maximum concentration, Tmax: time of maximum concentration

Observed PK parameters[3]		Predicted PK parameters		Ratio	
Cmax (µg/mL)	Tmax (h)	Cmax (µg/mL)	Tmax (h)	Cmax	Tmax
280	10	317	8.62	1.13	0.86

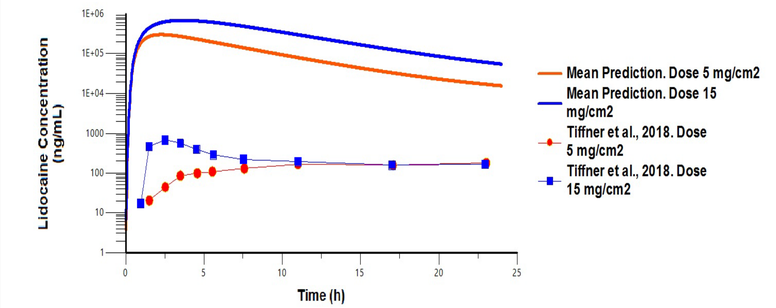

Figure 5: Predicted (mean, solid line) versus observed (mean, symbols) PK profiles of lidocaine in dermis following application of the lidocaine topical cream in healthy volunteers at two dose levels, 5 mg/cm^2 (red) and 15 mg/cm^2 (blue). Simulated profiles were generated utilizing the developed dermal PBPK model for lidocaine. Observed data were lidocaine concentrations in dermal interstitial fluid obtained by performing dermal open-flow microperfusion in healthy volunteers[22].

Conclusions

- ✓ **In vivo data collected in GDUFA-funded research have contributed towards the development of more versatile and reliable quantitative tools describing skin absorption for dermatological products.**
- ✓ **Systemic exposure following application of the Reference Listed Drugs for nicotine TDS, lidocaine topical cream and acyclovir topical cream was well predicted utilizing the developed dermal PBPK models.**
- ✓ **Skin bioavailability (dermis) of acyclovir and lidocaine following a single product application was overpredicted by the developed models.**

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