M2126

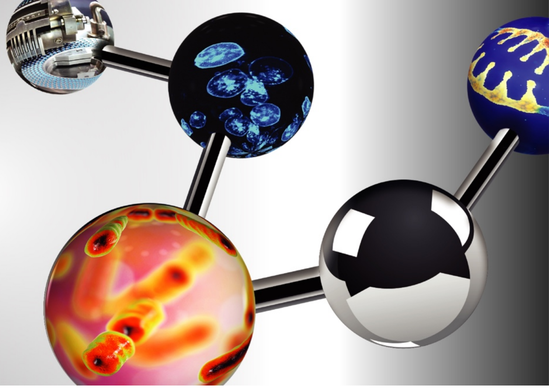
Modeling In Vitro and In Vivo Human Skin Permeation of Eutectic Mixtures of Local Anesthetics Using PBPK Modeling: Development of Dermal IVIVE for Lidocaine 2.5% w/w and Prilocaine 2.5% w/w Cream (EMLA® Cream)

K. C. Telaprolu[1], S. Polak[1, 2], E Tsakalozou[3], P. Ghosh[3], K. Alam[3], M. Dabbaghi[4], S. Namjoshi[4], Y. Mohammed[4], J. Grice[4], M.S. Roberts[4]

[1]Certara UK Ltd, Simcyp Division, Sheffield, UK; [2]Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland

[3]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), Silver Spring, MD, USA, [4]Therapeutics Research Centre, Diamantina Institute, University of Queensland, Brisbane, Queensland, Australia

CONTACT INFORMATION: krishna.chaitanyatelaprolu@certara.com



PURPOSE

The purpose of this work is to describe skin absorption of active ingredients from eutectic mixture formulations using the Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MPML MechDermA) in vitro skin permeation testing (IVPT) module within the Simcyp simulator (V20). An In Vitro – In Vivo Extrapolation (IVIVE) approach was used to derive critical kinetic parameters by modelling IVPT results of EMLA® cream (eutectic mixture of lidocaine 2.5% w/w and prilocaine 2.5% w/w) and the data were extrapolated towards the development of a Physiologically-Based Pharmacokinetic (PBPK) model to predict the systemic exposure of both lidocaine and prilocaine following topical application of the cream in humans.

METHOD(S)

The full-body PBPK models of lidocaine and prilocaine were developed by characterizing the distribution and elimination of both molecules from the pharmacokinetic (PK) data of intravenous (IV) bolus dosing [1, 2]. The developed models were validated using an external set of data of IV dosing [3, 4] as shown in Figure 1. Formulation-related parameters were collected from various literature sources and incorporated into the PBPK models to parametrize the emulsion model as shown in Table 1. IVPT data [5, 6] for EMLA® cream and plasma profiles following in vivo topical cream application were also collected [7]. The simulations of IVPT profiles were conducted by matching the experimental details (application site: abdomen; membrane type: epidermis; cell type: static) and were verified against experimental IVPT data [5, 6]. Partition and diffusion coefficients of both molecules in different skin layers were either predicted using Quantitative Structure Activity Relationships (QSAR) or experimentally measured (Table 2). Evaporation was assumed to be negligible as the IVPT experiments were carried out with partial occlusion and the thickness of the applied formulation was high. As both molecules are highly ionisable at skin surface pH, results are explained by manual optimization of formulation pH to 7.6 to calculate fraction non-ionized on the skin surface. This assumption of using formulation pH 7.6 was supported by Maurya et al. [8] where pH buffering of the applied formulation, when applied as thin film, is shown for products of various pH ranges. The in vitro model parameters were then used to extrapolate and predict in vivo scenarios accounting for all reported clinical study details such as the thigh as body site, and verified against systemic PK parameters [7]. For in vivo studies, native pH of formulation, i.e., 9.17, was used in the simulations as the study was conducted under occlusion conditions.

TABLE 1: Parametrization of emulsion model developed for the EMLA® cream in MPML MechDermA model

Parameter	Lidocaine	Prilocaine	Source of Information/Comment
Formulation Simulation Option	Emulsion, API fully dissolved	Emulsion, API fully dissolved	NA
Density of formulation (g/cm^3)	1	1	[7]
Viscosity @0.01-1 shear rate (cP)	1.62E+07	1.62E+07	Measured
Formulation pH	9.17	9.17	[5]
Drug Solubility in Continuous Phase (mg/mL)	3.52	6.67	Solubility at pH 10.35 [11]
Volume of Dispersed Phase (%)	5	5	[7]
Dispersed/Continuous Phase ratio	9	4.56	[9]
Droplet Size (µm)	0.109	0.109	[9]
Evaporation Profile	Not activated	Not activated	Study carried under occlusion
Precipitation Model	Not activated	Not activated	Study carried under occlusion

FIGURE 1: Observed (mean) and simulated plasma concentration profile of lidocaine (a) 1mg/kg of bolus dose [1]; and (b) 86.5 mg of bolus dose [3]; Observed (mean) and simulated plasma concentration profile of prilocaine (c) 214.5 mg IV infusion dose [2]; and (d) 200 mg IV bolus [4].

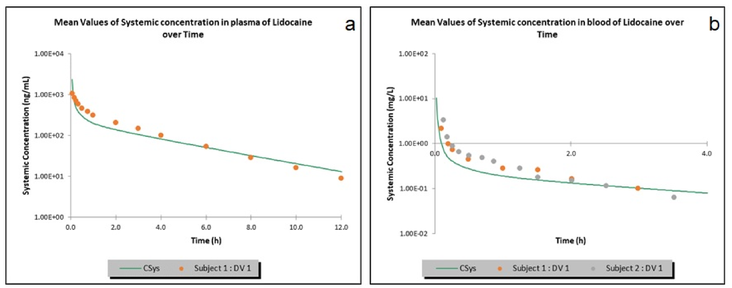


FIGURE 2: Observed (mean) versus predicted cumulative amount of lidocaine (µg) (A) and prilocaine (µg) (B) in receptor fluid from EMLA® cream using Fiala et al. 2016 [4] data.

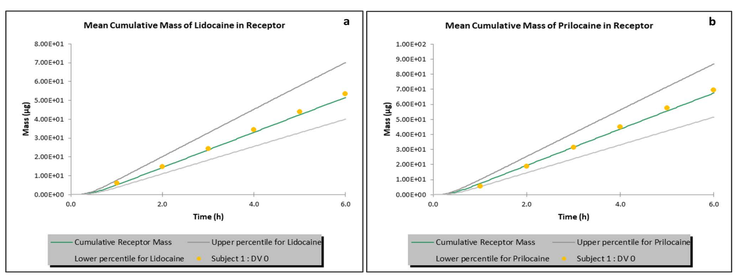


TABLE 2: Partition and diffusion coefficients of lidocaine and prilocaine used for both IVPT and in vivo simulations.

Parameter	Lidocaine	Prilocaine	Literature Source/QSAR
Partition Coefficients			
SC lipid: water Kp	23.99	29.33	Measured for Lidocaine and predicted by Hansen 2013* for Prilocaine
SC lipid: vehicle Kp	23.99	29.33	Predicted
Sebum: water Kp	52.07	35.89	Yang 2018*
Sebum: vehicle Kp	52.07	35.89	Predicted
SC: viable epidermis Kp	3.74	3.48	Shatkin and Brown 1991*
Dermis: viable epidermis Kp	0.22	0.25	Modified Chen 2015*
Dermis: sebum Kp	0.025	0.0279	Calculated
Receptor: membrane Kp	0.77	0.99	Modified Chen 2015* (Applies for IVPT only)
Dermis: blood Kp	1.993	1.77	Shatkin and Brown 1991*
Muscle: subcutis Kp	1		Model default
Blood: muscle Kp	1		Model default
Blood: subcutis Kp	1		Model default
Diffusion Coefficients			
SC lipid	0.000570	0.000603	Johnson 1996*
Viable epidermis	0.004257	0.00587	Modified Chen 2015*
Dermis	0.004257	0.00587	Modified Chen 2015*
Sebum	0.000694	0.00073	Johnson 1996*
Buffer	0.030	0.030	Schiebel 1995* (IVPT)
Subcutis	1E-05	1E-05	Model default
Muscle	1E-05	1E-05	Model default
Other Parameters			
fu_{sc} (Fraction Unbound in SC)	0.157	0.171	Polak et al. 2018 [10]
Corneocyte membrane permeability	1E-07	1E-07	Optimized
Fraction non-ionized in corneocytes	0.08	0.08	Predicted
Fraction non-ionized at skin surface	0.35 (IVPT) 0.95 (in vivo)	0.34 (IVPT) 0.95 (in vivo)	Assumption: using formulation pH as skin surface pH
Tortuosity	2584	2584	Johnson 1996*

*QSAR model.

TABLE 3a: Observed (mean, median for Tmax) versus predicted PK parameters of lidocaine following application of the EMLA® cream. The clinical PK study used for model performance assessment was described in the prescribing information. Simulation conditions were selected to mimic the clinical PK study.

Parameter	Observed	Predicted	Fold Error (predicted/observed)
Duration of Application 3 hours			
C_{max} (µg/mL)	0.12	0.13	1.1
T_{max} (hrs)	4	3.59	0.90
Amount absorbed (mg)	54	43.1	0.80
Duration of Application 24 hours			
C_{max} (µg/mL)	0.28	0.17	0.61
T_{max} (hrs)	10	10.02	1
Amount absorbed (mg)	243	223	0.92

TABLE 3b: Observed (mean, median for Tmax) versus predicted PK parameters of prilocaine following application of the EMLA® cream. The clinical PK study used for model performance assessment was described in the prescribing information. Simulation conditions were selected to mimic the clinical PK study.

Parameter	Observed	Predicted	Fold Error (predicted/observed)
Duration of Application 3 hours			
C_{max} (µg/mL)	0.07	0.13	1.86
T_{max} (hrs)	4	3.41	0.85
Amount absorbed (mg)	92	52.89	0.57
Duration of Application 24 hours			
C_{max} (µg/mL)	0.14	0.15	1.07
T_{max} (hrs)	10	5.70	0.57
Amount absorbed (mg)	503	265	0.53

TABLE 4: Predicted (Mean ± SD n = 40 10 trials of 4 individuals) versus observed flux (Mean ± SD n = 4 to 5) at two dosing conditions being within two-fold error

Dose of Drug (mg)	Flux (µg/cm^2/hr) Lidocaine			Flux (µg/cm^2/hr) Prilocaine		
	Observed	Predicted	Fold Error	Observed	Predicted	Fold Error
12.5	12.21 ± 1.81	15.81 ± 2.71	1.30	15.30 ± 2.15	20.44 ± 2.87	1.34
3	16.34 ± 0.83	15.55 ± 2.59	0.95	21.45 ± 1.31	20.06 ± 2.76	0.94

RESULT(S)

Figure 1 shows that distribution and elimination parameters used to describe the systemic disposition of Lidocaine and Prilocaine were able to predict internal (Figures 1a and 1c) and external datasets (Figures 2b and 2d). Figure 2 shows that the predicted in vitro cumulative receptor solution profile of EMLA® cream were matching the observed profiles for both molecules. In addition, the predictability of the model was further assessed using the same IVPT setup but under different dosing conditions. The predicted flux was within a 2-fold error (Predicted/Observed) as shown in Table 4. Tables 3a and 3b show that, the mean values of all the in vivo predicted primary PK parameters and drug amount absorbed were within the two-fold error of observed data for two application durations as described in the prescribing information for EMLA® cream [7].

CONCLUSION(S)

This study shows that skin permeation from eutectic mixtures can be predicted using in silico methodologies if drug product attributes are taken into account. The current study shows the utility of modelling IVPT experiments for mechanistic understanding, and interpreting the observed IVPT data. The key kinetic parameters derived by modelling IVPT experiments were used to predict the systemic pharmacokinetics and generate population predictions using the MPML MechDermA model. This dermal IVIVE approach may be used to predict drug permeation in the drug discovery setting, advance development of topical dermatological drug products and potentially in bioequivalence assessment for generic dermatological products.

REFERENCES

1. Orlando, R., et al., *Cytochrome P450 1A2 is a major determinant of lidocaine metabolism in vivo: effects of liver function.* Clin Pharmacol Ther, 2004. **75**(1): p. 80-8.
2. Simon, M.A., et al., *Comparison of the disposition kinetics of lidocaine and (+/-)prilocaine in 20 patients undergoing intravenous regional anaesthesia during day case surgery.* J Clin Pharm Ther, 1997. **22**(2): p. 141-6.
3. Bennett, P.N., et al., *Pharmacokinetics of lidocaine and its deethylated metabolite: dose and time dependency studies in man.* J Pharmacokinet Biopharm, 1982. **10**(3): p. 265-81.
4. Arthur, G.R., et al., *Pharmacokinetic and clinical pharmacological studies with mepivacaine and prilocaine.* Br J Anaesth, 1979. **51**(6): p. 481-5.
5. Fiala, S., et al., *New insights into eutectic cream skin penetration enhancement.* Int J Pharm, 2016. **499**(1-2): p. 403-411.
6. Fiala, S., M.B. Brown, and S.A. Jones, *Dynamic in-situ eutectic formation for topical drug delivery.* J Pharm Pharmacol, 2011. **63**(11): p. 1428-36.
7. Actavis Pharma, I. *EMLA CREAM (lidocaine 2.5% and Prilocaine 2.5%).* 2018 17/08/2016; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019941s021lbl.pdf.
8. A. Maurya, A.S., S.G. Raney, P. Ghosh, M.A. Repka, S.N. Murthy, *The pH of Topical Creams can Change Rapidly Following Application on the Skin In Vivo*, in *2016 AAPS Annual Meeting and Exposition*. 2016: Denver.
9. Nyqvist-Mayer, A.A., A.F. Brodin, and S.G. Frank, Phase distribution studies on an oil-water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed phase. J Pharm Sci, 1985. **74**(11): p. 1192-5.
10. Polak, S. & Patel, N.K. 2018. Combining machine learning and mechanistic modeling approaches to solve real life problems - assessment of the local tissue binding and its influence on the systemic exposure after topical application of drugs. American Conference on Pharmacometrics. Fort Lauderdale, Florida, USA.
11. Brodin, A., et al., Phase diagram and aqueous solubility of the lidocaine-prilocaine binary system. J Pharm Sci, 1984. **73**(4): p. 481-4.

This project was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award [FAIN] U01FD006522 totalling $250,000 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government. This poster reflects the views of the author and should not be construed to represent FDA's views or policies.